Journal of Molecular Catalysis A: Chemical 288 (2008) 103–108

Contents lists available at ScienceDirect

Journal of Molecular Catalysis A: Chemical

journal homepage: www.elsevier.com/locate/molcata

Synthesis of indole derivatives by domino hydroformylation/indolization of 2-nitrocinnamaldehydes

M. Marchetti[a,*], S. Paganelli[b], D. Carboni[a], F. Ulgheri[a], G. Del Ponte[c]

[a] Istituto di Chimica Biomolecolare, CNR, Sede di Sassari, traversa La Crucca 3, Località Baldinca, Li Punti, I-07049 Sassari, Italy
[b] Dipartimento di Chimica, Università Ca' Foscari di Venezia, Calle Larga S. Marta 2137, I-30123 Venezia, Italy
[c] Departamento de Ciências Farmacêuticas, Faculdade de Ciências Farmacêuticas de Ribeirão Preto, Universidade de São Paulo in Ribeirão Preto, Via do Café s/n, 14049 Ribeirão Preto, S.P., Brazil

ARTICLE INFO

Article history:
Received 27 July 2007
Received in revised form 5 March 2008
Accepted 12 March 2008
Available online 30 March 2008

Keywords:
Tandem hydroformylation
Indoles
Biologically active molecule intermediates
Rhodium
Indolization

ABSTRACT

The present work furnishes an innovative preparation of substituted indoles based on tandem hydroformylation, where the chemo- and the regio-selectivities are good, so the yield of the reaction. The novelty has been established in the four-step transformation of substituted alpha nitrocinnamaldehydes into desired indoles in a one-pot reaction. Under hydroformylation reaction conditions we have been able to trigger off a cascade of reactions, which gave substituted indoles in high yields. Useful intermediates are prepared by using this technique for the synthesis of well-known biologically active molecules.

1. Introduction

The indole nucleus is widespread in both natural and unnatural products. The interest in this skeletal structure is reflected by the numerous methodologies that have been devised and continue to be explored for its synthesis [1–12]. Indole and its myriad of derivatives continue to capture the attention of synthetic organic chemists, because the indole nucleus is present in many biologically active compounds as anti-inflammatory agents [13], antihypertensives [13,14], antitumoral [15], antiHIV [16], and antimigraine [17–22]. The worldwide demand for indole derivatives is about 20,000 t/year [23], e.g. tryptophan, an essential amino acid used as supplement for animal feeding, is produced in 100 t/year [24]. Moreover, indole derivatives are effective in the treatment of many psychiatric diseases like anxiety and depression; in this view new interesting studies on the neuropharmacological activity of omotriptamines have been developed [25,26]. Other valuable pharmaceuticals endowed with an indolic skeleton are the vasodilator Vintoperol [27] and the antiischemic Vinconate [28]. Indolyl derivatives are also active as integrate inhibitor of HIV-1 [15,29]. In the last several years, old antihypertensive indole derivatives as indoramine (*N*-[1-[2-(1H-indole-3-yl)ethyl]-4-piperidinyl]benzamide) [13,14] have also been evaluated as antagonist of adrenalinic receptors used in the treatment of prostatic disease [30]. Other important compounds derived from 3,5-substituted indoles are the indolebutylpiperazines, active as 5-HT_{1A}, receptor antagonist and seratonin reuptake inhibitors [31].

All these compounds are related to a molecular scaffold containing an indole moiety with appropriate substituents on the positions 3 and 5. Among the 3,5-substituted indole derivatives, one of the most versatile derivatives is represented by the acetaldehyde one **I**, due to the easy transformation of the carbonyl moiety into other functional groups (Fig. 1).

The importance of transition metal-based reagents in the synthesis and functionalization of indoles [11,32] is well known and owing to our interest in the application of the hydroformylation process to the synthesis of fine chemicals [33–42], we aimed to prepare the indole nucleus by domino hydroformylation of vinyl aromatic nitro derivatives. It is known that *o*-nitrostyrene is transformed, by rhodium-catalyzed hydroformylation, into 3-methylindole; however, the oxo process is carried out under drastic conditions (160 °C at 160 atm of syngas) and the chemoselectivity proved to be unsatisfactory [43]. Also 3-methylindole was obtained by rhodium-catalyzed tandem hydroformylation, starting from *o*-aminostyrene obtained by reduction of *o*-nitrostyrene [44]. Some different substituted indoles, such as tryptamines and tryptophol, have been pre-

* Corresponding author.
E-mail address: mauro@ss.cnr.it (M. Marchetti).

1381-1169/$ – see front matter © 2008 Elsevier B.V. All rights reserved.
doi:10.1016/j.molcata.2008.03.025

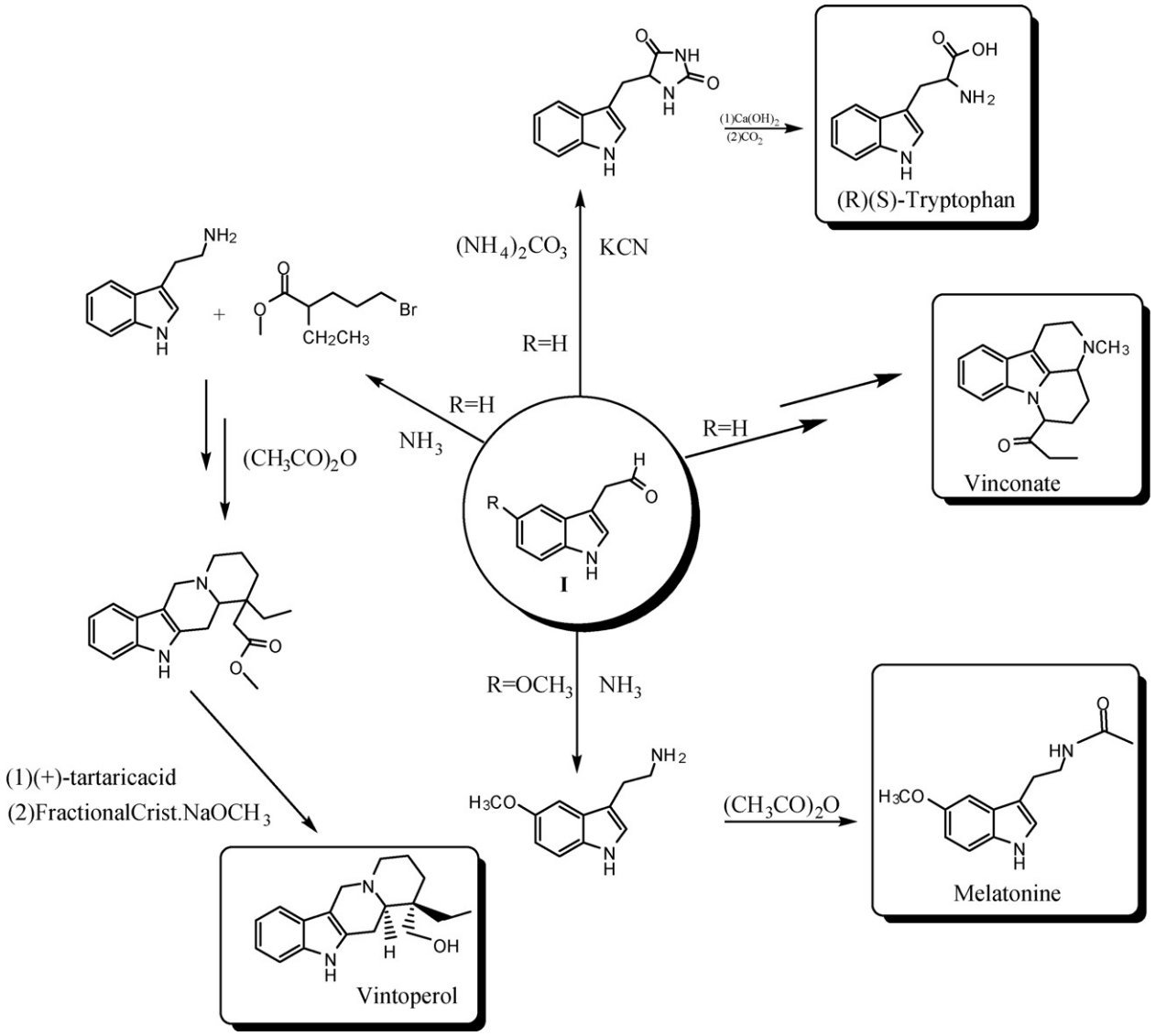


Fig. 1. Examples of synthetic routes to bioactive compounds starting from 3-indolylacetaldehyde (I) and 5-substitued 3-indolylacetaldehyde.

pared by hydroformylation of functionalyzed anilines; however, the hydroformylation yield at the best reaches about 70%; moreover, all the obtained products, except tryptophol, were only amines [45]. *N*-Acetyl-5-methoxytryptamine (melatonin) has been obtained in 44% yield by rhodium-catalyzed hydroformylation of *N*-allylacetammide, either in aqueous or biphasic medium, followed by hydrazone formation with 4-methoxyphenylhydrazine and Fischer indole synthesis [46]. More recently, substituted indoles, such as tryptophan, melatonin, serotonin, etc., have been prepared by a tandem hydroformylation/Fischer indole synthesis starting from olefins and arylhydrazine [47,48]. Moreover, many pharmacologically relevant indoles were synthesised by tandem hydroformylation/hydrazone formation/Fischer indole synthesis starting from amino olefins or allyl amides [49–51].

Since many biologically active compounds are 3,5-substituted indole derivatives containing the acetaldehydo moiety in the 5 position [11], we decided to hydroformylate *m*-substituted-*o*-nitrocinnamaldehyde diethyl acetal to obtain the desired scaffold which can be transformed into various pharmaceuticals (Fig. 1).

2. Experimental

2.1. General remarks

2-Nitrocinnamaldehyde was purchased from Aldrich. $Rh(CO)_2(acac)$ and $HRh(CO)(PPh_3)_3$ were obtained from strem. Flash chromatographies were carried out on silica gel Merck 60, 230–400 mesh. ^1H NMR spectra were recorded on a Varian Mercury Plus 400 MHz, using $CDCl_3$ as solvent. GC analysis was carried out on an Agilent 6850A gas chromatograph, using an HP1 column (30 m × 0.32 mm × 0.25 μm). GC–MS analysis was performed by using an Agilent MS Network 5937 equipped with an HP-5MS column (30 m × 0.25 mm × 0.25 μm). Solvents were purified as described in the literature [52].

2.1.1. Preparation of 2-nitrocinnamaldehyde diethyl acetal (1)

1.01 g (5.69 mmol) of 2-nitrocinnamaldehyde, 20 mL of absolute EtOH and 20 mL of cyclohexane were placed into a reaction vessel equipped with a reflux apparatus in which were placed dried molecular sieves 4 A; the molecular sieves were held by compressed glass wool. To the reaction mixture were added 119 mg (0.11 equiv.)

of *p*-TsOH and 500 mg of anhydrous Na_2SO_4. The reaction mixture was refluxed for 12 h. To the cooled mixture were added 2 g of solid $NaHCO_3$, the solvents were evaporated and the residue was washed three times with 20 mL of methylene dichloride. The solution was washed three times using a saturated solution of $NaHCO_3$ (pH > 8), and dried over anhydrous Na_2SO_4 and the solvent was evaporated. The yield based on crude reaction product was 96%. The crude product was purified by flash chromatography using hexane/ethyl ether 7:3 as eluant. The yield of purified **1** was 90%.

^{1}H NMR ($CDCl_3$) δ (ppm), J (Hz): 7.89–7.86 (dd, J_{max} = 8 Hz, J_{min} = 1.2 Hz, 1H); 7.62–7.58 (m, 2H); 7.37–7.32 (dt, 1H); 7.13–7.09 (d, J_{max} = 16 Hz, 1H); 6.11–6.06 (dd, J_{max} = 15.8 Hz, J_{min} = 5 Hz, 1H); 5.08 (dd, J_{max} = 5 Hz, J_{min} = 1 Hz, 1H); 3.70–3.50 (dq, J_{max} = 56.2 Hz, J_{min} = 7.0 Hz, 2H); 3.67–3.48 (dq, J_{max} = 56.2 Hz, J_{min} = 7.4 Hz, 2H); 1.19 (t, J = 7.0 Hz, 6H).

^{13}C NMR ($CDCl_3$) δ (ppm): 133.13, 132.15, 131.96; 128.83; 128.48; 128.36; 124.54; 101.03, 61.53, and 15.23.

GC–MS *m*/*e*: 250 $[M-H]^+$.

2.1.2. Synthesis of 2-(5-methoxy-2-nitrostyryl)-1,3-dioxolane (6)

The synthesis of **6** has been carried out in three steps:

(a) Preparation of 5-methoxy-2-nitrobenzaldehyde by reaction of commercially available 5-methoxy-2-nitrobenzoic acid (Fluka) with $NaBH_4$ [53], followed by oxidation with $Na_2Cr_2O_7$ [54]. The desired aldehyde was obtained in 74% overall yield.
^{1}H NMR ($CDCl_3$), δ (ppm), J (Hz): 10.48 (s, 1H); 8.18–8.14 (d, J = 8.54, 1H); 7.34–7.12 (m, 2H); 3.96 (s, 3H).

(b) Preparation of 1,3-dioxolan-2-yl-methyltriphenylphosphonium salt by following a known procedure [55]; the desired phosphonium salt was obtained in 71% yield starting from 2-(bromomethyl)-1,3-dioxolane (m.p. 192–193 °C).

(c) The desired compound **6** was obtained by Wittig reaction of 5-methoxy-2-nitrobenzaldehyde with the above-cited phosphonium salt following the experimental procedure described by Daubresse et al. [56]. The overall yield based on 5-methoxy-2-nitrobenzaldehyde was 81%. The crude reaction product was purified by flash chromatography on silica gel using hexane/ethyl ether 7:3 as eluant. Pure **6** was recovered in 75% yield.

Compound **6**: ^{1}H NMR ($CDCl_3$) δ (ppm), J (Hz): 8.32–8.30 (d, J = 8.0, 1H); 7.66 (s, 1H); 7.30–7.26 (d, J = 15.2, 1H); 6.15–6.10 (dd, J_{max} 16.0, J_{min} = 5.2, 1H); 5.50–5.48 (dd, J_{max} = 5.6, J_{min} = 0.8, 1H); 4.09–3.97 (m, 2H); 4.07–3.99 (m, 2H); 3.93 (s, 3H).

^{13}C NMR ($CDCl_3$) δ (ppm): 165.80, 141.35, 130.26; 128.30; 128.18; 125.36; 118.54; 114.87, 113.03, 66.53, and 57.90.

GC–MS *m*/*e*: 250 $[M-H]^+$.

2.1.3. Synthesis of 2-(5-chloro-2-nitrostyryl)-1,3-dioxolane (9)

Compound **9** was obtained by Wittig reaction between 2-(bromomethyl)-1,3-dioxolane and 5-chloro-2-nitrobenzaldehyde [56]. The yield based on purified compound was 67%.

^{1}H NMR ($CDCl_3$) δ (ppm), J (Hz): 8.72–8.70 (d, J = 8.4, 1H); 7.82 (s, 1H); 7.50–7.46 (d, J = 15.9, 1H); 6.15–6.10 (dd, J_{max} = 15.9, J_{min} = 4.8, 1H); 5.70–5.68 (dd, J_{max} = 5.6, J_{min} = 0.8, 1H); 4.49–4.37 (m, 2H); 4.28–4.16 (m, 2H).

^{13}C NMR ($CDCl_3$) δ (ppm): 145.80, 140.35, 129.10; 128.90; 128.70; 127.36; 125.44; 124.57, 115.13, 64.53.

2.1.4. General tandem hydroformylation procedure

A 150 mL stainless steel reaction vessel was charged under nitrogen with 3.0 mmol of substrate, 0.01 mmol of the catalytic precursor and 5 mL of anhydrous toluene (see tables). The reactor was then pressurized with 80–100 atm of syngas (CO/H_2 = 1), heated to 80–120 °C for the due time (see tables), and then cooled to room temperature and the gases were vented off. For analytical purposes the target products were recovered from the reaction mixture by flash silica gel chromatography (*n*-hexane/ether, 8/2).

Compound **3**: ^{1}H NMR ($CDCl_3$) δ (ppm), J (Hz): 9.80 (d, J = 7.6 Hz, 1H); 7.66–7.64 (m, 1H); 7.35–7.33 (m, 1H); 7.25–7.01 (m, 1H); 6.71–6.65 (m, 2H); 4.43 (t, J = 6.7 Hz, 1H); 3.72–3.67 (m, 2H); 3.68–3.48 (m, 2H); 3.09 (dd, J_{max} = 23.0 Hz, J_{min} = 6.7 Hz, 2H); 2.6 (m, 1H); 2.06 (m, 2H); 1.20 (m, 6H).

MS: *m*/*e* 280 $[M]^+$; 253; 206; 190; 162; 146; 134; 116; 104; 91; 77; 65; 51.

Compound **5**: ^{1}H NMR ($CDCl_3$) δ (ppm), J (Hz): 8.19–8.10 (sb, 1H); 7.65 (d, J = 8 Hz, 1H); 7.34 (d, J = 8 Hz, 1H); 7.25–7.01 (m, 1H); 6.71–6.65 (m, 2H); 4.76 (t, J = 5.6 Hz, 1H); 3.72–3.67 (m, 2H); 3.68–3.48 (m, 2H); 3.09 (dd, J_{max} = 5 and 8 Hz, J_{min} = 0.6 Hz, 2H); 1.2 (t, J = 7.0 Hz, 6H).

^{13}C NMR ($CDCl_3$) δ (ppm): 135, 127, 122, 121, 119, 118, 111, 110, 103, 62, 61, 30, and 15.

MS: *m*/*e* 233 $[M]^+$, 188, 158, 144, 130, 103, 91, 77, 65 and 51.

Compound **7**: ^{1}H NMR ($CDCl_3$) δ (ppm), J (Hz): 9.26 (d, J = 1.7, 1H); 8.34–8.32 (d, J = 8.0, 1H); 7.66 (s, 1H); 7.32–7.29 (d, J = 15.2, 1H); 5.03–4.99 (m, 1H); 4.36–4.31 (m, 1H); 3.82–3.81 (m, 2H); −3.79 to 3.78 (m, 2H); 3.73 (s, 3H); 2.14–2.10 (d, J = 7.45, 2H).

MS: *m*/*e* 280 $[M]^+$, 250, 219, 162, 103, 91, 77, 65, and 51.

Compound **8**: ^{1}H NMR ($CDCl_3$) δ (ppm), J (Hz): 7.10–7.00 (m, 3H); 6.91 (s, 1H); 5.03–4.99 (m, 1H); 3.81 (s, 3H); 3.84–3.72 (m, 4H); 3.13–3.11 (dd, J_{max} = 4.8, J_{min} = 0.9, 2H).

MS: *m*/*e* 232 $[M]^+$, 202, 160, 129, 115, 87, 73 and 31.

Compound **10**: ^{1}H NMR ($CDCl_3$) δ (ppm), J (Hz): 9.34 (d, J = 1.5, 1H); 8.56–8.51 (m, 2H); 7.94 (d, J = 8.4, 1H); 5.03–4.99 (m, 1H); 3.99–3.94 (t, J = 7.4, 1H); 3.79–3.78 (m, 4H); 2.12–2.08 (dd, J_{max} = 7.40, J_{min} = 4.8, 2H).

MS: *m*/*e* 286 $[M]^+$, 256, 250, 239, 156, 129, and 121.

Compound **11**: ^{1}H NMR ($CDCl_3$) δ (ppm), J (Hz): 7.68 (s, 1H); 7.18–7.15 (d, J = 9.2, 1H); 7.12–7.09 (d, J = 9.2, 1H); 7.00 (s, 1H); 5.05–5.02 (m, 1H); 3.78–3.74 (m, 4H); 3.11–3.10 (dd, J_{max} = 4.7, J_{min} = 1.0, 2H).

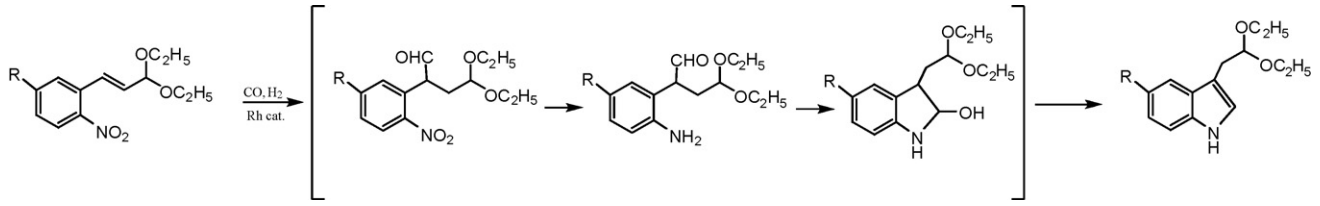
MS: *m*/*e* 238 $[M]^+$, 202, 164, 152, 129, 115, 87, 73 and 31.

3. Results and discussion

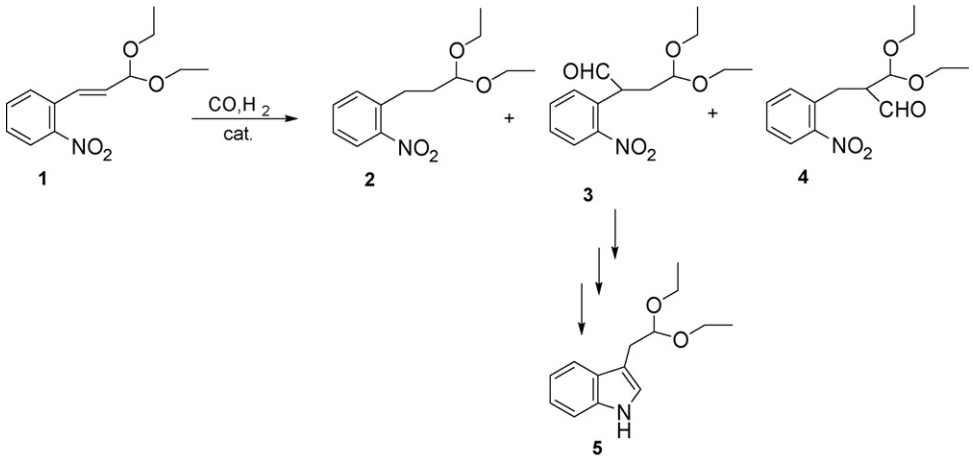
A domino reaction involves two or more bond-forming transformations, which take place under the same reaction conditions, without adding additional reagents and catalysts, and in which the subsequent reactions result as a consequence of the functionality formed by bond formation or fragmentation in the previous step [57]. The domino hydroformylation/indolization of 2-nitrocinnamaldehydes for the synthesis of (1H-indol-3-yl)-acetaldehyde derivatives, important scaffolds for several pharmacologically active compounds, requires efficient hydroformylation, reduction of the nitro group and intramolecular amino reduction under optimised conditions (Scheme 1).

In this view, first we undertook the study of the domino hydroformylation/indolization of 2-nitrocinnamylaldehyde diethyl acetal **1**, chosen as model substrate (Scheme 2).

The results depicted in Table 1 show that rhodium catalytic precursors were very efficient while cobalt and platinum-based catalysts gave very poor chemoselectivities, high boiling by-products being the prevailing reaction products (runs 1 and 2). In the presence of $Rh(CO)_2(acac)$ at 120 °C and 80 atm of syngas (CO/H_2 = 1) for 24 h, the substrate conversion was almost complete but the main product was 2-nitrodihydrocinnamaldehyde diethyl acetal (**2**); nevertheless, 47% of the desired indole **5** was also formed (run 3). By lowering the reaction temperature to 80 °C, indole **5** was obtained in 83% yield but also in this case, a significant amount



Scheme 1. Domino hydroformylation/indolization of 2-nitrocinnamaldehyde acetales.



Scheme 2. Hydroformylation of 2-nitrocinnamaldehyde diethyl acetal (1).

Table 1
Hydroformylation of 2-nitrocinnamaldehyde diethyl acetal (**1**)

Run	Catalyst	T (°C)	t (h)	P (atm)	Conversion (%)	**2** (%)	**3** (%)	**4** (%)	**5** (%)
1[a]	$Co_2(CO)_8$	120	24	100	99	15	8	2	–
2[b]	(BZN)$PtCl_2$/L1[c]	120	24	100	70	–	2	3	–
3	$Rh(CO)_2(acac)$	120	24	80	99	52	–	–	47
4	$Rh(CO)_2(acac)$	80	24	80	99	16	–	–	83
5	$HRh(CO)(PPh_3)_3$	80	33	80	80	–	59	–	21
6	$HRh(CO)(PPh_3)_3$	80	63	80	100	–	39	–	61
7	$HRh(CO)(PPh_3)_3$	80	115	80	100	–	20	–	80
8	$HRh(CO)(PPh_3)_3$	80	136	80	100	–	6	–	94
9	$HRh(CO)(PPh_3)_3$	80	168	80	100	–	–	–	>99

Substrate = 3 mmol; substrate/catalyst (molar ratio) = 300/1; solvent (toluene) = 5 mL; $p(CO) = p(H_2)$.

[a] 74% of high boiling by-products was found in the reaction mixture.

[b] 65% of high boiling by-products was found in the reaction mixture.

[c] L1 = $SnCl_2$/1,3-bis(diphenylphosphino)propane. Pt/$SnCl_2$/1,3-bis(diphenylphosphino)propane = 1:2:1.

of hydrogenated substrate **2** was detected in the reaction mixture (run 4). In both cases, no traces of aldehydes **3** or **4** were found. $Rh(CO)_2(acac)$ (runs 3 and 4) proved to be very efficient in promoting aldehyde **3** formation and its subsequent cyclization to the corresponding indole **5** but it was not possible to suppress the undesired substrate hydrogenation. In order to prevent this side reaction and to improve the chemoselectivity of the process, we drew our attention to a phosphine modified rhodium carbonyl complex; in particular, we chose $HRh(CO)(PPh_3)_3$, a well-known chemoselective catalyst in the oxo-process [58]. Indeed, this catalytic precursor, under the above reaction conditions, showed very high chemo- and regio-selectivities; substrate hydrogenation of the C=C double bond was absent and aldehyde **3** was the only oxo-product. Unfortunately, the sought indolization reaction occurred to a quite small extent, indole **5** being formed in 20% yield (run 5). By prolonging the reaction time the formation of **5** strongly increased up to 100% after 168 h at 80 °C and 80 atm of syngas ($CO/H_2 = 1$) (run 9) (Fig. 2).

Applying the catalytic precursors and the reaction conditions above described, we attempted to hydroformylate

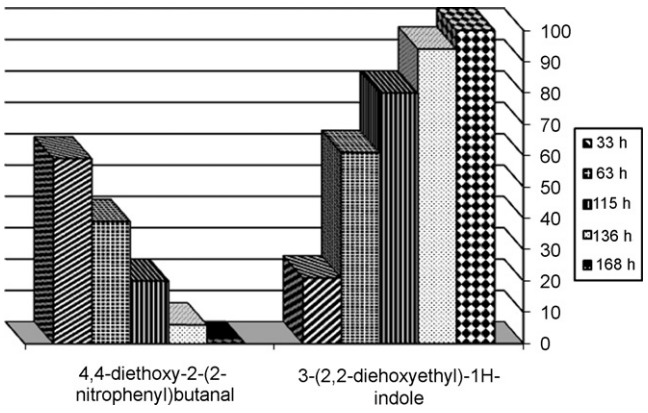
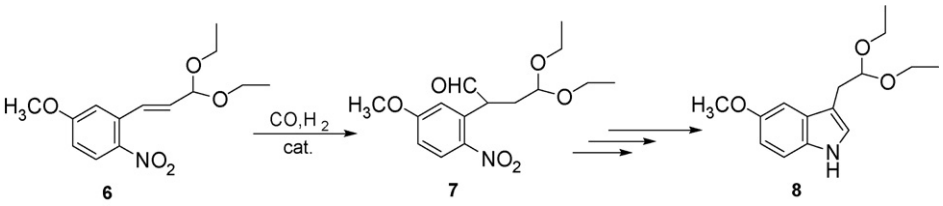
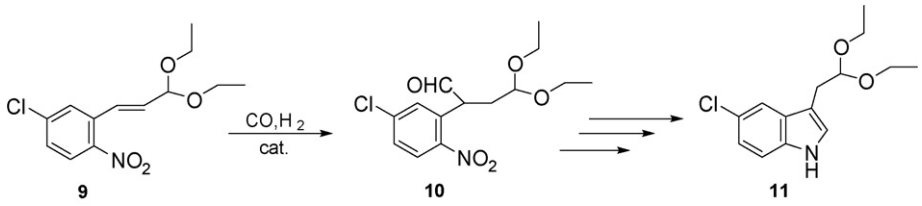


Fig. 2. Effect of the reaction time in the formation of the indole **5**.



Scheme 3. Hydroformylation of 2-(5-methoxy-2-nitrostyryl)-1,3-dioxolane (6).



Scheme 4. Hydroformylation of 2-(5-chloro-2-nitrostyryl)-1,3-dioxolane (9).

2-(5-methoxy-2-nitrostyryl)-1,3-dioxolane (**6**) aiming to synthesise a valuable precursor of melatonine in a one-pot domino hydroformylation–indolization. The reaction is depicted in Scheme 3.

The substrate was prepared by Wittig reaction [56] of 5-methoxy-2-nitrobenzaldehyde with 1,3-dioxolan-2-yl-methyltriphenylphosphonium salt [55] in 75% yield.

The results obtained in the hydroformylation experiments, described in Table 2, resemble the data obtained in 2-nitrocinnamaldehyde diethyl acetal hydroformylation; the chemoselectivity was always complete and the formation of the indole derivative **8** strongly dependent on the reaction time. In fact, although compound **8** was obtained in only 38% yield after 48 h (run 2), by prolonging the reaction time up to 240 h the indole derivative yield was complete (run 5). By comparing the results obtained in the hydroformylation of substrates **1** and **6**, we can observe that the presence of the methoxy group in the 5-position of the aromatic ring of **6** decreases the indolization rate. We can suggest that the electron donor substituent has a detrimental effect on the hydrogenation of a nitro group in the *para* position, so lowering the rate of formation of the intermediate amino derivative. As a matter of fact, it is known that electron-donor groups, which tend to increase the electron density on the nitro function and thereby to lower the polarization of the N—O bonds, lead to lower rates of hydrogenation [59]. On the basis of this result we have to take into account also an alternative reaction pathway, recently reported by Cenini and his co-workers [60,61]. They observed that the reductive carbonylation of nitroarenes initially produced nitrosoarenes and that the reduction was accelerated by electron-withdrawing substituents; this could explain the lower reaction rate when a methoxy group is present on the substrate.

Table 2
Hydroformylation of 5-methoxy-2-nitrocinnamaldehyde diethyl acetal (**6**) catalyzed by $HRh(CO)(PPh_3)_3$

Run	*t* (h)	Conversion (%)	**7** (%)	**8** (%)
1	24	56	46.5	9.5
2	48	100	62	38
3	120	100	40	60
4	180	100	18	82
5	240	100	–	100

Substrate = 3 mmol; substrate/catalyst (molar ratio) = 300/1; solvent (toluene) = 5 mL; $p(CO) = p(H_2) = 40$ atm; temperature = 80 °C.

Table 3
Hydroformylation of 5-chloro-2-nitrocinnamaldehyde diethyl acetal (**9**) catalyzed by $HRh(CO)(PPh_3)_3$

Run	*t* (h)	Conversion (%)	**10** (%)	**11** (%)
1	24	68	61	7
2	48	100	65	35
3	120	100	52	48
4	180	100	15	85
5	240	100	–	100

Substrate = 3 mmol; substrate/catalyst (molar ratio) = 300/1; solvent (toluene) = 5 mL; $p(CO) = p(H_2) = 40$ atm; temperature = 80 °C.

Comparable results, reported in Table 3, were obtained also in the hydroformylation of 2-(5-chloro-2-nitrostyryl)-1,3-dioxolane (**9**) (Scheme 4) synthesized as above described for compound **6**.

Also in this case also the yield of **11** was improved by prolonging the reaction time, reaching a complete yield after 240 h (run 5).

3.1. Conclusive remarks

This work presents an innovative route to the preparation of substituted indoles, based on a very selective tandem hydroformylation process. In particular, substituted alpha-nitrocinnamaldehydes can be transformed into the sought indoles by a one-pot four-step reaction. In fact, under hydroformylation reaction conditions, the substrate undergoes cascade reactions which lead to the formation of the substituted heterocycle. By using this synthetic route we have been able to prepare useful intermediates for the synthesis of well-known biologically active compounds containing the indole moiety in their molecular skeleton.

References

[1] S. Wagaw, B.H. Yang, S.L. Buchwald, J. Am. Chem. Soc. 120 (1998) 6621.
[2] A.J. Peat, K. Aoki, S.L. Buchwald, J. Am. Chem. Soc. 120 (1998) 3068.
[3] S. Wagaw, B.H. Yang, S.L. Buchwald, J. Am. Chem. Soc. 121 (1999) 10251.
[4] G.W. Gribble, J. Chem. Soc., Perkin Trans. I (2000) 1045.
[5] A.V. Butin, T.A. Stroganova, I.V. Lodina, G.D. Krapivin, Tetrahedron Lett. 42 (2001) 2031.
[6] A. Klapars, J.C. Antilla, X.H. Huang, S.L. Buchwald, J. Am. Chem. Soc. 123 (2001) 7727.
[7] O. Miyata, Y. Kimura, T. Naito, Synthesis (2001) 1635.
[8] A. Penoni, J. Volkmann, K.M. Nicholas, Org. Lett. 4 (2002) 699.
[9] A. Penoni, K.M. Nicholas, Chem. Commun. (2002) 484.
[10] S.J. Garden, R.B. da Silva, A.C. Pinto, Tetrahedron 58 (2002) 8399.
[11] G.R. Humphrey, J.T. Kuethe, Chem. Rev. 106 (2006) 2875.
[12] S. Patil, J.K. Buolamwini, Curr. Org. Synth. 3 (2006) 477.
[13] J. Rochus, Merck & Co., DE19531463 (1997).

[14] J.L. Neumeyer, U.V. Moyer, J.E. Leonard, J. Med. Chem. 12 (1969) 450.
[15] G. Cirrincione, A.M. Almerico, P. Barraja, P. Diana, A. Lauria, A. Passannanti, C. Musiu, A. Pani, P. Murtas, C. Minnei, M.E. Marongiu, P. La Colla, J. Med. Chem. 42 (1999) 2561.
[16] C.A. Sotriffer, H. Ni, J.A. Mac Cammon, J. Med. Chem. 43 (2000) 4109.
[17] D. Forner, C.P. Duran, J.P. Soto, A.V. Noverala, Almirall, US 5,565,447 (1996).
[18] R. Baker, L.J. Street, V.G. Matassa, Merck & Co., EP 497512 (1992).
[19] W. Kraus, A. Weisert, Glaxo, DE 3320521. (1983).
[20] D. A. Robertson, Wellcome, WO 9118897. (1991).
[21] B.E. Mondell, Clin. Therapeut. 25 (2003) 331.
[22] J. Gras, J. Bou, J. Llenas, A.G. Fernandez, J.M. Palacios, Eur. J. Pharmacol. 410 (2000) 43.
[23] F. Conti, Chim. Ind. 87 (2005) 94.
[24] H.H. Szmant, Organic Building Blocks of the Chemical Industry, John Wiley & Sons, New York, 1989, p. 338.
[25] P.R. Brodfuehrer, B.-Chi Chen, T.R. Sattelberg Sr., P.R. Smith, J.P. Reddy, D.R. Stark, S.L. Quinlan, J.G. Reid, J.K. Thottathil, S. Wang, J. Org. Chem. 62 (1997) 9192.
[26] D.J. Denhart, R.J. Mattson, J.L. Ditta, J.E. Macor, Tetrahedron Lett. 45 (2004) 3803.
[27] K. Orito, T. Imaizumi, K. Yoshida, H. Fujiki, M. Kishi, S. Teramoto, M. Tanaka, H. Shimizu, M. Tominaga, Y. Kimura, J. Kambayashi, T. Mori, J. Pharmacol. Exp. Ther. 291 (1999) 604.
[28] T. Iino, M. Katsura, K. Kuriyama, Eur. J. Pharmacol. 286 (1995) 99.
[29] Y. Goldgur, R. Craigie, G.H. Cohen, T. Fujiwara, T. Yoshinaga, T. Fujishita, H. Sugimoto, T. Endo, H. Murai, D.R. Davies, Proc. Natl. Acad. Sci. U.S.A. 96 (1999) 13040.
[30] P. Boyle, C. Roehrborn, R. Harkaway, J. Logie, J. de la Rosette, M. Emberton, Eur Urol. 45 (2004) 620.
[31] R. Tao, Z. Ma, S.B. Auerbach, J. Pharmacol. Exp. Ther. 294 (2000) 571.
[32] L.S. Hegedus, Angew. Chem. Int. Ed. Engl. 27 (1988) 1113.
[33] C. Botteghi, M. Marchetti, S. Paganelli, in: C. Bolm, M. Beller (Eds.), Transition Metals for Organic Synthesis, 1, VCH, Weinheim, 1998.
[34] C. Botteghi, M. Marchetti, S. Paganelli, F. Persi-Paoli, Tetrahedron 57 (2001) 1631.
[35] C. Botteghi, C. Dei Negri, S. Paganelli, M. Marchetti, J. Mol. Catal. A: Chem. 175 (2001) 1725.
[36] M. Marchetti, S. Scognamillo, S. Paganelli, C. Botteghi, J. Mol. Catal. A: Chem. 179 (2002) 79.
[37] C. Botteghi, T. Corrias, M. Marchetti, S. Paganelli, O. Piccolo, Org. Proc. Res. Dev. 6 (2002) 379.
[38] C. Botteghi, S. Paganelli, F. Moratti, M. Marchetti, R. Lazzaroni, R. Settambolo, O. Piccolo, J. Mol. Catal. A: Chem. 200 (2003) 147.
[39] M. Marchetti, S. Paganelli, E. Viel, J. Mol. Catal. A: Chem. 222 (2004) 143.
[40] S. Paganelli, L. Spano, M. Marchetti, O. Piccolo, Chim. Ind. 87 (2005) 94.
[41] S. Paganelli, F. Battois, M. Marchetti, R. Lazzaroni, R. Settambolo, S. Rocchiccioli, J. Mol. Catal. A: Chem. 246 (2006) 195.
[42] S. Paganelli, A. Ciappa, M. Marchetti, A. Scrivanti, U. Matteoli, J. Mol. Catal. A: Chem. 247 (2006) 138.
[43] E. Ucciani, A. Bonfand, J. Chem. Soc., Chem. Commun. (1981) 82.
[44] T.J. Kwok, D.J. Wink, Organometallics 12 (1993) 1954.
[45] Y. Dong, C.A. Busacca, J. Org. Chem. 62 (1997) 6464.
[46] G. Verspui, G. Elberste, F.A. Sheldon, M.A.P.J. Hacking, R.A. Sheldon, Chem. Commun. (2000) 1363.
[47] P. Köhling, A.M. Schmidt, P. Eilbracht, Org. Lett. 5 (2003) 3213.
[48] M. Ahmed, R. Kackstell, A.M. Seayad, H. Klein, M. Beller, Tetrahedron Lett. 45 (2004) 869.
[49] A.M. Schmidt, P. Eilbracht, J. Org. Chem. 70 (2005) 5528.
[50] A.M. Schmidt, P. Eilbracht, Org. Biomol. Chem. 3 (2005) 2333.
[51] P. Linnepe, A.M. Schmidt, P. Eilbracht, Org. Biomol. Chem. 4 (2006) 302.
[52] D.D. Perrin, L.F. Armarego, Purification of Laboratory Chemicals, 3rd ed., Pergamon Press, Oxford, 1998.
[53] M. Falorni, A. Porcheddu, M. Taddei, Tetrahedron Lett. 40 (1999) 4395.
[54] D. Pletcher, S.J. Jait, J. Chem. Soc., Perkin Trans. II (1979) 778.
[55] T.H. Cresp, M.V. Sargent, P. Vogel, J. Chem. Soc., Perkin Trans. I (1974) 37.
[56] N. Daubresse, C. Franceschi, C. Rolando, Tetrahedron 54 (1998) 10761.
[57] L.F. Tietze, Chem. Rev. 96 (1996) 115.
[58] P.W.N.M. van Leeuwen, C.P. Casey, G.T. Whiteker, in: P.W.N.M. van Leeuwen, C. Claver (Eds.), Rhodium-Catalyzed Hydroformylation., Kluwer Acad. Publ., Dordrecht, 2000.
[59] J.F. Knifton, J. Org. Chem. 41 (1976) 1200.
[60] F. Ragaini, S. Cenini, E. Gallo, A. Caselli, S. Fantauzzi, Curr. Org. Chem. 10 (2006) 1479.
[61] F. Ragaini, A. Rapetti, E. Visentin, M. Monzani, A. Caselli, S. Cenini, J. Org. Chem. 71 (2006) 3748.