



ELSEVIER

Journal of Molecular Catalysis A: Chemical 111 (1996) 91–96

**JOURNAL OF  
MOLECULAR  
CATALYSIS  
A: CHEMICAL**

# Transition metal-mediated N-heterocyclisation reactions. Synthesis of 2-phenylindole by reduction by CO of 2-nitrostilbene catalysed by $[\text{Rh}(\text{CO})_4]^-$

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Received 4 March 1996; accepted 24 May 1996

## Abstract

The complex  $[\text{PPN}][\text{Rh}(\text{CO})_4]$  is a very efficient catalyst for the conversion of 2-nitrostilbene to 2-phenylindole by reduction by CO followed by cyclisation. The reaction is quite selective (up to 85%) and the only observable by-product is the amine corresponding to the starting material. The addition of 2-hydroxypyridine increases both conversion and selectivity, but simple pyridine deactivates the catalytic system. The reaction conditions have been optimised.

**Keywords:** Indoles; Organic nitro compounds; Rhodium; Rhodium tetracarbonyl anion; Homogeneous catalysis; Heterocycles; N-Heterocyclisation reactions

## 1. Introduction

The indole nucleus is present in a large number of biologically active compounds [1]. Besides the 'classical' organic synthetic methodology, transition-metal-assisted methods have been developed for both the synthesis and the functionalisation of indoles [1]. One of the most useful involves the catalytic deoxygenation of *ortho*-nitrostyrenes by carbon monoxide [2–8]. Only two papers have reported on the use of rhodium complexes as catalysts for this reaction [2,3] and the reaction reported in one of these [3] is not simply a deoxygenation of the nitro

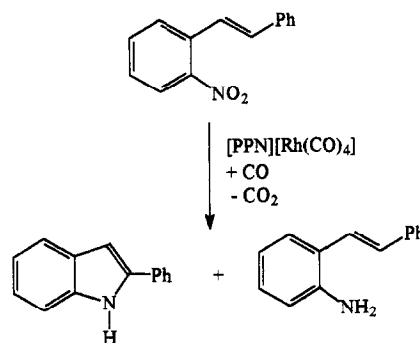
group, but an hydroformylation of the olefinic group by  $\text{CO}/\text{H}_2$ , followed by condensation of the so formed aldehyde with the amino group derived from hydrogenation of the nitro group. Research in our group [2] has shown that  $\text{Rh}_6(\text{CO})_{16}$  is a catalyst for the synthesis of indoles from nitrostyrenes, but reaction conditions were quite severe, the catalytic ratio low (8.3 with respect to the rhodium atoms) and the selectivity only moderate (highest 58.8%). In recent years, we have shown that  $[\text{Rh}(\text{CO})_4]^-$  (1) (often used as its  $\text{PPN}^+$  salt,  $\text{PPN}^+ = (\text{PPh}_3)_2\text{N}^+$ ) is a better catalyst than other mononuclear or cluster complexes for deoxygenation and carbonylation reactions of nitroarenes and it appears to be the active species even when these other complexes are used as catalyst precursors [9–12]. We thus considered

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that  $[\text{Rh}(\text{CO})_4]^-$  may afford better results than other rhodium compounds even in the field of the synthesis of heterocyclic products by deoxygenation of nitroarenes bearing in the *ortho* position suitable substituents. To the best of our knowledge,  $[\text{Rh}(\text{CO})_4]^-$  has never been used before in any such reaction. In this paper, we report on the synthesis of 2-phenylindole by reduction by CO of 2-nitrostilbene, chosen as a model substrate. The results show that a marked improvement in both activity and selectivity is obtained upon use of this anionic catalyst with respect to the use of  $\text{Rh}_6(\text{CO})_{16}$  as catalyst precursor.

## 2. Results and discussion

The complex  $[\text{PPN}][\text{Rh}(\text{CO})_4]$  (**1**) has been found to be a very efficient catalyst for the conversion of 2-nitrostilbene, chosen as a model substrate, to 2-phenylindole. The reaction is quite selective (up to 85%) and the only observable by-product is the amine corresponding to



the starting material, although minor amounts of polymeric products must also be formed in order to account for the mass balance (Scheme 1).

The results of a partial optimisation study of the reaction conditions are reported in Table 1. Since the same complex had already been used by us to catalyse the related carbonylation reaction of nitrobenzene in the presence of methanol, to afford methyl phenylcarbamate ( $\text{PhNHCOOMe}$ ) [9–11], we examined some of the modifications found to be effective in this

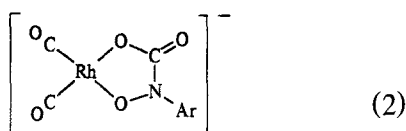
Table 1  
Synthesis of 2-phenylindole by carbonylation of 2-nitrostilbene catalysed by  $[\text{PPN}][\text{Rh}(\text{CO})_4]$ <sup>a</sup>

Run	Solvent (ml)	Cocatalyst (mol ratio cocat./cat.)	<i>T</i> (°C)	<i>P</i> <sub>CO</sub> (atm)	Conv. (%)	Select. indole (%) <sup>b</sup>	Select. amine (%) <sup>b</sup>
1	THF (10)	—	170	60	71.0	58.0	21.1
2	THF (10)	pyridine (6)	170	60	42.5	57.4	34.0
3	THF (9.5) + MeOH (0.5)	—	170	60	90.3	13.9	75.4
4	THF (9.5) + MeOH (0.5)	pyridine (6)	170	60	64.2	45.9	43.9
5	THF (10)	2-OH-pyridine (6)	170	60	88.0	64.3	28.1
					86.6	69.9	23.5
6	THF (9.5) + MeOH (0.5)	2-OH-pyridine (6)	170	60	95.2	54.0	43.9
7	THF (10)	4-OH-pyridine (6)	170	60	55.1	57.5	29.7
8	DMF (10)	2-OH-pyridine (6)	170	60	100	45.7	48.4
9	DME (10)	2-OH-pyridine (6)	170	60	48.8	62.6	29.2
10	<i>o</i> -Cl <sub>2</sub> C <sub>6</sub> H <sub>4</sub> (10)	2-OH-pyridine (6)	170	60	66.4	82.5	8.4
11	<i>o</i> -Cl <sub>2</sub> C <sub>6</sub> H <sub>4</sub> (10)	2-OH-pyridine (6)	180	60	72.8	75.8	15.5
12	<i>o</i> -Cl <sub>2</sub> C <sub>6</sub> H <sub>4</sub> (10)	2-OH-pyridine (6)	160	60	60.1	74.1	20.2
13	<i>o</i> -Cl <sub>2</sub> C <sub>6</sub> H <sub>4</sub> (10)	2-OH-pyridine (6)	170	40	62.3	65.2	25.2
14	<i>o</i> -Cl <sub>2</sub> C <sub>6</sub> H <sub>4</sub> (10)	2-OH-pyridine (6)	170	80	64.8	85.1	9.7
15	<i>o</i> -Cl <sub>2</sub> C <sub>6</sub> H <sub>4</sub> (10)	2-OH-pyridine (12)	170	60	58.9	77.9	15.7
16	<i>o</i> -Cl <sub>2</sub> C <sub>6</sub> H <sub>4</sub> (10)	2-OH-pyridine (3)	170	60	72.6	78.3	17.9
17	<i>o</i> -Cl <sub>2</sub> C <sub>6</sub> H <sub>4</sub> (10)	—	170	60	63.4	65.6	31.2

<sup>a</sup> Experimental conditions:  $[\text{PPN}][\text{Rh}(\text{CO})_4] = 0.020$  mmol, stilbene = 1.00 mmol, *t* = 5 h. DMF = N,N-dimethylformamide, DME = 1,2-dimethoxyethane.

<sup>b</sup> Calculated with respect to the converted substrate.

latter reaction. In particular, it had been found that the addition of an organic nitrogen base (pyridine, bipyridine, triethylamine or methylimidazole) greatly enhanced the catalytic activity. Moreover, the presence of an alcohol was essential to observe a reaction. At least one role of the alcohol was to react with an intermediate metallacyclic complex (2), allowing for the proceeding of the reaction.

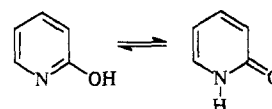


Metallacyclic complexes analogous to complex (2) may be formed even in this case and the presence of a protic reagent may be important in promoting the reaction, even if it is not included in the final product.

Addition of pyridine to the reaction mixture, however, only resulted in a decreased conversion (runs 1, 2), whereas the selectivity in indole was not altered. The addition of methanol, on the other hand, sensibly increased the conversion, but the largely dominant product was now the amine, with only 13.9% of the indole being formed (run 3). The addition of both pyridine and methanol resulted in a lower conversion and a higher selectivity with respect to the addition of methanol alone, but the observed values are worst than those observed if neither methanol nor pyridine are added (runs 4, 1). These results suggest that some differences exist between the mechanism of the carbonylation of nitrobenzene to methyl phenylcarbamate and the present reaction, even in the early stages of the reactions which may be common to both the catalytic cycles.

For reasons that will be detailed elsewhere [13], we suspected that 2-hydroxypyridine may

be a good promoter for the present heterocyclisation reaction. Indeed, the addition of a small amount (6:1 with respect to the catalyst) of this substance to the reaction mixture sensibly increased both conversion and selectivity, independently by the presence of methanol (compare runs 5 with 1 and 6 with 3). The effect is clearly due to the close disposition of the nitrogen and hydroxyl groups, rather than to some effect due to the known tautomeric equilibrium between 2-hydroxypyridine and its pyridonic form (Eq. 1) [14],



since the addition of 4-hydroxypyridine, for which the same equilibrium exists, actually inhibited, rather than promote, the reaction (run 7).

Contrary to the use of  $[\text{PPN}][\text{Rh}(\text{CO})_4]$  (1) as catalyst for the related carbonylation reaction of nitrobenzene [9–11], toluene was not an effective solvent in the present reaction. Only a very poor conversion and tarry products were obtained. This is probably due to the complete insolubility of the ionic 1 in this apolar solvent. In the synthesis of carbamates, the large amounts of nitrobenzene and methanol ( $\sim 4$  and 3 ml) with respect to toluene (8 ml) renders the mixture homogeneous, whereas the lower catalytic ratio and the solid nature of the starting material in the present case do not allow for this positive solubilisation effect. Several polar solvents gave however positive results. Among those tested (all in the presence of 2-hydroxypyridine), the conversion increased in the order 1,2-dimethoxyethane (DME) <  $o\text{-Cl}_2\text{C}_6\text{H}_4$  < THF < DMF (runs 5, 8–10) but the selectivity in indole followed the order DMF < DME < THF <  $o\text{-Cl}_2\text{C}_6\text{H}_4$ . Clearly, DMF affords the best activity, but the worst selectivity. The best solvent concerning selectivity is  $o\text{-Cl}_2\text{C}_6\text{H}_4$ , although

only a medium conversion was achieved in this medium. Since we deemed selectivity was more important than activity in this reaction, we optimised the experimental conditions with respect to this last solvent (runs 10–17). An higher temperature, 180°C, increases the conversion but lowers the selectivity (run 11). On the other hand, a lower temperature (160°C) lowers both conversion and selectivity (run 12). By increasing the CO pressure (80 bar) the highest selectivity (85.1%) was obtained, although the conversion decreased slightly (run 14). This behaviour is quite common in catalytic carbonylation reactions and is attributed to the need for a vacant coordination site at some stage during the reaction. A lower pressure (40 bar) led to an only slightly lower conversion, but the selectivity dropped (run 13).

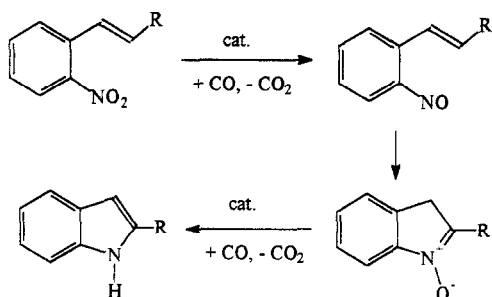
We finally optimised the amount of 2-hydroxypyridine added (runs 10, 15–17). By varying the 2-hydroxypyridine/Rh molar ratio between 0 and 12, it is possible to evidence a bell-shaped pattern for both conversion and selectivity, with the best ratios being 3 for what it concerns conversion and 6 for what it concerns selectivity. It should be noted that the addition of 2-hydroxypyridine causes smaller variations in *o*-Cl<sub>2</sub>C<sub>6</sub>H<sub>4</sub> as solvent than in THF, but an effect is still clearly evident.

These results are much better than those previously obtained by use of Rh<sub>6</sub>(CO)<sub>16</sub> as catalyst and better even of those obtained by use of Fe(CO)<sub>5</sub> [2], Ru<sub>3</sub>(CO)<sub>12</sub> [2,5], and PdCl<sub>2</sub>(PPh<sub>3</sub>)<sub>2</sub>/SnCl<sub>2</sub> [6,7], although the selectivity is inferior to the one obtained by us with the Pd(2,4,6-trimethylbenzoate)<sub>2</sub>/3,4,7,8-tetramethyl-1,10-phenanthroline catalytic system [8].

Some attempts were made to isolate intermediate complexes. As previously mentioned, we had previously found that [PPN][Rh(CO)<sub>4</sub>] reacts with nitrobenzene or substituted nitrobenzenes to yield a metallacyclic complex 2 in which the metallacycle is composed by the nitrosoarene and CO<sub>2</sub> fragments, whose structure has been solved by X-ray crystallography in the case of Ar = 3,4-Cl<sub>2</sub>C<sub>6</sub>H<sub>3</sub> [11,12]. However,

attempts to generate the same type of metallacyclic complex starting from 2-nitrostilbene failed. Working under one atmosphere of CO, no reaction was observed up to a temperature (~60°C) at which complete decomposition of the rhodium complex was observed. Even by repeating the same reaction under CO pressure, no metallacycle could be isolated and the organic substrate was partly converted to indole. Apparently, the initial activation of the nitroarene, which is very likely to occur through an electron transfer from the complex to the nitro compound [10,11], is rate-determining. Thus, we can only speculate about the reaction mechanism. Formation of a nitrene complex is the most often proposed hypothesis and deoxygenation of 2-nitrostyrenes by P(OEt)<sub>3</sub> has long been known to afford indole derivatives [15–20]. Deoxygenation reactions of nitro compounds by P(OEt)<sub>3</sub> are traditionally believed to proceed through the intermediate formation of nitrene species (see later for an alternative explanation). However, when the carbonylation of some organic nitro derivatives was conducted in *cis*-cyclooctene as solvent and with Ru<sub>3</sub>(CO)<sub>12</sub> as catalyst, nitrenes have been detected among the products [21]. Under these conditions, the intermediate nitroso derivative reacts with the alkene solvent to yield the corresponding nitrene. The reaction of nitroso derivatives with alkenes is in fact one of the methods for the preparation of nitrenes [22] and the reaction of nitrosobenzene with styrene proceeds even at 0°C, despite its *inter*-molecular nature [23]. One may expect the *intra*-molecular cyclisation of an intermediate 2-nitrostilbene to be even faster. Thus it could be that in the case of the carbonylation of *ortho*-nitrostyrenes, the reaction follows the path depicted in Scheme 2.

The intermediate nitroso derivative gives the nitrene before being deoxygenated. Deoxygenation of the latter then leads to the final product. This last reaction is expected to be very easy, since deoxygenation of the related trialkylamine-N-oxides and azoxyarenes by metal carbonyl complexes are well known reactions. In



Scheme 2.

our system, the instability of the presumable intermediate metallacycle analogous to 2, suggests that the cyclisation is indeed proceeding from the nitrosoarene intermediate. However, the formation of an imido intermediate would better explain the formation of the corresponding amine, which is always formed together with the indole derivatives. It is possible that the amine is formed from an imido complex formed by deoxygenation of some nitroso compound in competition with cyclisation. In the context of this discussion, it is interesting to remark that, even in the case of the related cyclisation reactions promoted by  $P(OEt)_3$ , the formation of a nitroso intermediate is extremely likely and, despite this possibility appears to have never been considered before, there is no evidence that the reaction proceeds further to the free nitrene rather than following a path analogous to the one in Scheme 2, with  $P(OEt)_3$  being responsible for the final deoxygenation of the nitrene species.

### 3. Experimental section

#### 3.1. General procedure

All reactions were conducted under a nitrogen or CO atmosphere using either a standard Schlenk apparatus or an autoclave (see also later). Solvents were dried by standard procedures, degassed and stored under nitrogen before use. Nitrostilbene [24] and  $[PPN][Rh(CO)_4]$  [25] were synthesised by literature methods. All other reagents were commercial products and

were used as received. Gas chromatographic analyses were performed on a Perkin-Elmer 8420 gas chromatograph (PSS 255 capillary column), for quantitative analysis, or on a Hewlett Packard 5890 gas chromatograph equipped with a 5971A mass selective detector for confirmation of products identities. For the purpose of quantitative analysis, response factors (relative to naphthalene as an internal standard) were determined by use of solutions of known concentrations of the pure compounds, obtained by separating the collected reaction mixtures of several catalytic reactions by flash chromatography (silica, eluent  $CH_2Cl_2$ ). The identity of the isolated samples was confirmed by comparison of the  $^1H$  NMR spectra, mass spectra and gas chromatographic retention times with those of authentic samples.

#### 3.2. Catalytic reactions

In a typical reaction, 2-nitrostilbene (224 mg, 1.00 mmol),  $[PPN][Rh(CO)_4]$  (15.0 mg, 0.02 mmol), and, possibly, 2-hydroxypyridine (see Table 1), were weighed in a glass liner. The liner was placed inside a Schlenk tube with a wide mouth, evacuated and filled with nitrogen, after which the solvent and, possibly, other liquid reagents (see Table 1) were added. The liner was frozen at  $-78^\circ C$  with dry ice, rapidly transferred to a 200 ml stainless steel autoclave with magnetic stirring, and the autoclave was evacuated and filled with nitrogen three times. CO was then charged at room temperature at the required pressure. Other experimental conditions are reported in Table 1. At the end of the reaction the autoclave was cooled with an ice bath, vented and the products were analysed by gas chromatography (naphthalene as an internal standard).

#### Acknowledgements

We thank Italian CNR, Progetto Strategico Tecnologie Chimiche Innovative, for financial support.

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