Intermediate formation of anilines in the synthesis of Schiff bases from nitroarenes and aldehydes

Fabio Ragaini *, Sergio Cenini

Dipartimento di Chimica Inorganica, Metallorganica e Analitica and CNR Center, Via G. Venezian 21, I-20133 Milan, Italy

Abstract

The role of the intermediate formation of anilines in the synthesis of Schiff bases from nitroarenes, aldehydes and CO catalysed by metal complexes has been investigated. Contrary to earlier belief, the reaction does not proceed through the reaction of an intermediate nitrene with the carbonyl compound, but by reduction of the nitroarene by CO and traces of water to initially afford the aniline, which then reacts with the aldehyde to afford the Schiff base, regenerating the water necessary to reduce more nitroarene. © 1999 Elsevier Science B.V. All rights reserved.

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1. Introduction

Schiff bases are important chemicals and the imine group is present in a large number of natural and synthetic products [1]. Most synthetic procedures for these products employ an amine and an aldehyde as starting materials and a suitable procedure is often necessary to remove the formed water and shift the equilibrium towards the products (Eq. (1)):

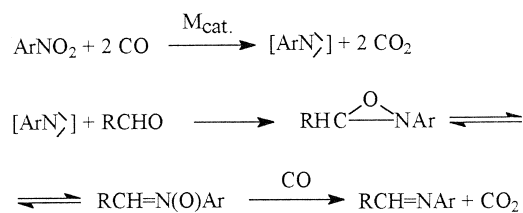$$RNH_2 + R'CHO \rightleftharpoons RN{=}CR' + H_2O \tag{1}$$

As an alternative to the use of amines and dehydrating agents, it has long been known that Schiff bases can also be obtained by condensation of an aldehyde with a nitroarene under reducing conditions (Eq. (2)) [2]:
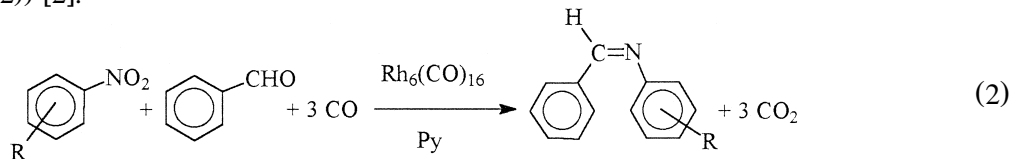
Dry pyridine as solvent and $Rh_6(CO)_{16}$ as catalyst were used, at 150 atm and 170°C. Yields were 60–85%, whereas only 5–7% Schiff base formation took place in benzene as solvent. Other metal

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* Corresponding author. Tel.: +39-2-26680675; Fax: +39-2-2362748; E-mail: ragaini@mail.csmtbo.mi.cnr.it

$$ArNO_2 + 2\ CO \xrightarrow{M_{cat.}} [ArN\rangle] + 2\ CO_2$$

$$[ArN\rangle] + RCHO \longrightarrow RHC\overset{O}{\diagdown}NAr \rightleftharpoons$$

$$\rightleftharpoons RCH{=}N(O)Ar \xrightarrow{CO} RCH{=}NAr + CO_2$$

Scheme 1.

carbonyls such as $Fe(CO)_5$, $Ru_3(CO)_{12}$ and $Co_2(CO)_8$ can be used as catalysts. Other complexes later employed for the same reaction are $PdCl_2Py_2$ (Py = pyridine) as catalyst with Py as co-catalyst [3], $PdCl_2(PPh_3)_2$ in the presence of $SnCl_2$ [4], and selenium in the presence of a base [5]. The formation of Schiff bases by the intramolecular condensation of a nitroarene with an aldehyde is also an intermediate step in the synthesis of a number of heterocycles from nitroarenes bearing in the *ortho* position a substituent including a carbonyl group [6].

For all of the aforementioned reactions, a nitrene intermediate was considered to be the reactive intermediate able to condense with the carbonyl group (note that the nitrene, if formed, is almost surely coordinated to the metal) (Scheme 1).
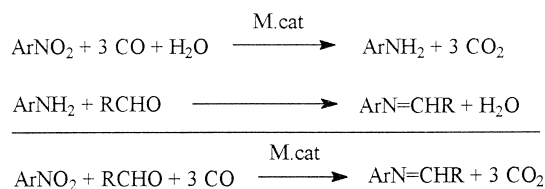
In a control experiment it was proved that the nitrone, RCH=N(O)Ar, gives the Schiff base by reaction with CO at 130 atm and 150°C in the presence of $Rh_6(CO)_{16}$ [2].

The intermediate formation of amines, which could give the Schiff base according to reaction (1) was excluded, since no water was formed. However, we have already suggested [7] that the water so formed may easily react with the starting nitroarene and CO to generate more aniline. Reduction of nitroarenes by CO and water is known to be catalysed by many metal complexes with a high efficiency [7]. Thus water would act as a catalyst and would not accumulate up to a detectable extent (Scheme 2).

In this paper, we report evidence in favour of the correctness of our proposal, showing the importance of the presence of trace amounts of water in order for the reaction to proceed.

2. Results and discussion

The best way to decide if anilines are intermediates in the condensation reaction of a nitroarene with an aldehyde would be to run this last reaction in the presence of an aniline bearing on the aromatic ring a substituent different from the one on the nitroarene. In this case, selective formation of the Schiff base deriving from the nitroarene should be observed were the nitrene the only active intermediate, whereas a mixture of the two possible Schiff bases should be observed in case aniline were an intermediate. Unfortunately, control experiments showed that Schiff bases exchange the

$$ArNO_2 + 3\ CO + H_2O \xrightarrow{M.cat} ArNH_2 + 3\ CO_2$$

$$ArNH_2 + RCHO \longrightarrow ArN{=}CHR + H_2O$$

$$\overline{\phantom{ArNO_2 + RCHO + 3\ CO \xrightarrow{M.cat} ArN{=}CHR + 3\ CO_2}}$$

$$ArNO_2 + RCHO + 3\ CO \xrightarrow{M.cat} ArN{=}CHR + 3\ CO_2$$

Scheme 2.

imido fragment with external anilines even at temperatures lower than the one necessary for the condensation reaction from the nitroarene to proceed. Thus we had to investigate the effect of small additions of water to carefully dried solvent mixtures more quantitatively.

Iqbal has reported the use of $Rh_6(CO)_{16}$ in pyridine for the condensation reaction of nitroarenes with aldehydes (Eq. (2)) [2], however work by Fachinetti et al. [8] has shown that pyridine induces a disproportionation reaction of rhodium clusters and work in our group [9,10] has shown that $[Rh(CO)_4]^-$ is the most active species in all rhodium-catalysed reductive carbonylation reactions of nitroarenes. Thus we decided to directly employ $[PPN][Rh(CO)_4]$ ($PPN^+ = (PPh_3)_2N^+$) as catalyst, which allowed us to use milder conditions than those originally reported and to avoid the use of very polar solvents, which are difficult to dry.

The catalytic condensation of nitrobenzene and benzaldehyde was conducted in dichlorobenzene at 170°C and under 60 bar CO, taking much care that all reagents and solvent were carefully dried and the reaction was then repeated by adding 10 and 20 μl of water respectively. Results are reported in Table 1.

As it is evident from the results reported, not only the reaction is very slow in the absence of added water, but even the selectivity is very poor and more aldehyde is consumed than nitroarene to afford high boiling products that could not be observed by gas chromatography. In the presence of 10 μl of water, the nitrobenzene conversion doubled and the amount of converted aldehyde was almost perfectly equivalent to the one of nitrobenzene. Even more interestingly, the selectivity in Schiff base increased as much as from 20 to 75% (based on nitrobenzene conversion; even more, from 12 to 79% with respect to converted aldehyde), despite some aniline was also observable in this case. An increase in the water amount (20 μl) further increased the conversion, but more aniline was formed and the selectivity lowered with respect to the second reaction, still being much higher than the one of the reaction in the absence of added water.

By plotting the nitrobenzene conversion against the amount of water (Fig. 1) a straight line is obtained ($R^2 = 0.972$) indicating a first order dependency of the conversion on the water concentration. The intercept is not zero, however, it has to be realised that even if carefully dried solvents and liquid reagents were used, the employed CO contains small amounts of water and dihydrogen. Thus, even in the first experiments, a very small amount of aniline is surely formed anyway.

As a second system, we decided to investigate the $PdCl_2(PPh_3)_2$–$SnCl_2$ combination, as this has also been employed in the synthesis of heterocyclic compounds [4]. Experiments similar to the ones described for $[PPN][Rh(CO)_4]$, but with 1,4-dioxane as solvent, were performed under the conditions of Ref. [4] and the results are reported in Table 2.

Table 1
Effect of the water amount on the coupling reaction of nitrobenzene with benzaldehyde catalysed by $[Rh(CO)_4]^{-a}$

Run	H_2O (μl)	$PhNO_2$ conversion (%)[b]	PhCHO conversion (%)[c]	Schiff base selectivity (%)		$PhNH_2$ selectivity (%)[d]
				/$PhNO_2^d$	/$PhCHO^e$	
1	0	9.0	14.8	20.5	12.4	< 1
2	10	17.7	17.2	75.0	77.9	12.8
3	20	33.5	26.1	45.1	59.1	20.2

[a]Experimental conditions: $[PPN][Rh(CO)_4] = 6.64 \times 10^{-2}$ mmol, molar ratios $Rh/PhNO_2/PhCHO = 1/200/200$, at 170°C and 60 bar CO for 1.5 h, in *o*-dichlorobenzene (10 ml).
[b]Calculated with respect to initial $PhNO_2$.
[c]Calculated with respect to initial PhCHO.
[d]Calculated with respect to converted $PhNO_2$.
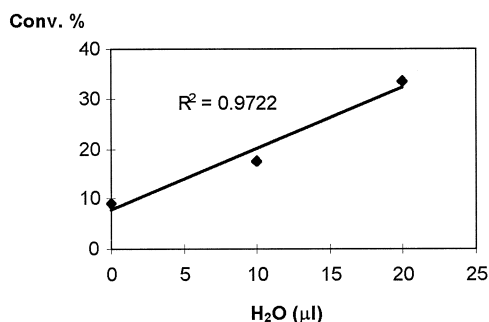[e]Calculated with respect to converted PhCHO.

Fig. 1. Effect of the water amount on the nitrobenzene conversion in the synthesis of phenylbenzimine catalysed by [PPN][Rh(CO)$_4$].

Even in this case, the same effect is observed as for the rhodium-catalysed reactions. The linearity of the correlation between nitrobenzene conversion and water amount is even higher for this second catalytic system ($R^2 = 0.988$) (Fig. 2). A non-zero intercept is again observed, for which the same explanation previously given for the rhodium system can be proposed.

Overall, we consider the aforementioned experiments a strong evidence in favour of the involvement of aniline in the catalytic cycle, that is the process in Scheme 2 is supported against the one in Scheme 1. Although it cannot be completely excluded that the non-zero intercept in the Figs. 1 and 2 is due at least in part to the reaction pathway in Scheme 1, this pathway appears anyway to play at best a limited role. Note that this study does not imply that imido (nitrene) complexes are surely not formed during the reaction as no information has been gained on which is the complex responsible for aniline formation. What we have shown is that *in case an imido complex is formed*, this will react with water in favour of benzaldehyde, affording aniline.

Clearly the ideal amount of water is a delicate balance of the always positive effect of larger amounts of water on conversion and of the bell shaped form of the water/selectivity curve. This last effect is most striking in the case of rhodium. In this case a 4.2% water with respect to the nitroarene is sufficient to increase the selectivity from 20.5 to 75.0%, but a 8.4% amount lowers it back to 45.1%. It is clear that a small amount of water may easily be present in completely non-dried solvents and even reagents and this must be taken in mind when performing similar reactions.

As previously mentioned, Schiff base formation is also an intermediate step in the synthesis of several heterocycles, for example quinolines, from *o*-substituted nitroarenes. Nitrenes have been most often held responsible for these cyclisation reactions, but it now appears that anilines are probably

Table 2

Effect of the water amount on the coupling reaction of nitrobenzene with benzaldehyde catalysed by PdCl$_2$(PPh$_3$)$_2$–SnCl$_2$[a]

Run	H$_2$O (µl)	PhNO$_2$ conversion (%)[b]	PhCHO conversion (%)[c]	Schiff base selectivity (%)		PhNH$_2$ selectivity (%)[d]
				/PhNO$_2$[d]	/PhCHO[e]	
1	0	20.3	36.0	81.5	41.2	3.9
2	10	48.8	46.5	86.6	76.2	4.2
3	20	68.3	60.9	77.9	76.3	8.5

[a]Experimental conditions: PdCl$_2$(PPh$_3$)$_2$ = 0.10 mmol, molar ratios Pd/SnCl$_2$/PhNO$_2$/PhCHO = 1/10/21/25, at 100°C and 20 bar CO for 4 h, in 1,4-dioxane (10 ml).
[b]Calculated with respect to initial PhNO$_2$.
[c]Calculated with respect to initial PhCHO.
[d]Calculated with respect to converted PhNO$_2$.
[e]Calculated with respect to converted PhCHO.
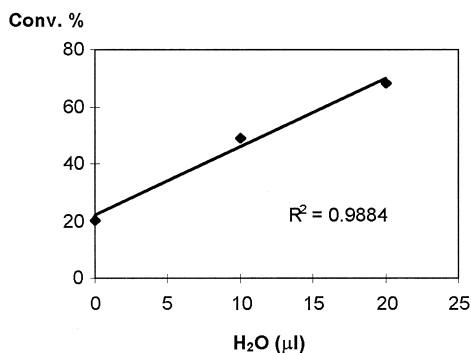
Fig. 2. Effect of the water amount on the nitrobenzene conversion in the synthesis of phenylbenzimine catalysed by $PdCl_2(PPh_3)_2 - SnCl_2$.

formed even in these cases. We are currently investigating the role of the intermediate formation of anilines in the synthesis of several kinds of heterocycles and the results will be reported in a forthcoming paper [11].

3. Experimental

3.1. General procedures

Unless otherwise specified, all reactions and manipulations were performed under a N_2 atmosphere using standard Schlenk apparatus, cannula techniques, and magnetic stirring, but the products of the catalytic reactions had to be handled in the air for at least some time. o-Dichlorobenzene (CaH_2) and 1,4-dioxane (Na) were dried and distilled by standard procedures and stored under dinitrogen. Benzaldehyde was distilled and stored under dinitrogen before use. Water was degassed by three freeze–pump–thaw cycles. Nitrobenzene was purified by shaking with 10% H_2SO_4, washing with water, and drying with Na_2SO_4, followed by distillation under dinitrogen and storage under an inert atmosphere. [PPN][Rh(CO)$_4$] [12] and $PdCl_2(PPh_3)_2$ [13] were synthesised by methods reported in the literature. All other compounds were commercial products and were used as received. Gas chromatographic analyses were performed on a Perkin-Elmer 8420 capillary gas chromatograph equipped with a PS 255 column. R_i values (R_i = response factor, relative to naphthalene as an internal standard) were determined by the use of solutions of known concentrations of the compounds. GC–MS analyses were performed on a Hewlett-Packard 5890 Series II gas chromatograph, equipped with a 5971A mass selective detector. NMR spectra were recorded on a Bruker AC 200 FT spectrometer (200 MHz) at RT. Elemental analyses and mass spectra were recorded in the analytical laboratories of Milan University.

3.2. Catalytic reactions

In a typical reaction, the reagents (see Tables 1 and 2) were weighed in a glass liner. The liner was placed inside a Schlenk tube with a wide mouth under dinitrogen. The liner was frozen at $-78°C$ with dry ice, evacuated and filled with dinitrogen, after which the solvent was added. After the solvent was also frozen, the liner was closed with a screw cap having a glass wool-filled open mouth which allows for gaseous reagents exchange and rapidly transferred to a 200 ml stainless steel

autoclave with magnetic stirring. The autoclave was then evacuated and filled with dinitrogen three times. CO was then charged at room temperature at the required pressure. In the case of the reactions catalysed by [PPN][Rh(CO)$_4$], to avoid contact with air of this sensitive compound, it was weighed under dinitrogen and added to the glass liner only after the liner had already been frozen in the Schlenk tube under dinitrogen. Other experimental conditions are reported in Tables 1 and 2. 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

References

[1] F.A. Carey, R.J. Sundberg, Advanced Organic Chemistry, 3rd edn., Plenum, New York, 1993.
[2] A.F.M. Iqbal, J. Org. Chem. 37 (1972) 2791.
[3] S. Suzuki, Jpn. Kokai 76,136,631 (1976), Chem. Abstr. 87 (1976) 5639w.
[4] M. Akazome, T. Kondo, Y. Watanabe, Chem. Lett. (1992) 769.
[5] R. Tsumura, T. Abe, Jpn. Kokai 77 25,725 (1977), Chem. Abstr. 87 (1977) 134459m.
[6] S. Cenini, F. Ragaini, Catalytic Reductive Carbonylation of Organic Nitro Compounds, Chap. 5, Kluwer Academic Press, Dordrecht, 1997, and references therein.
[7] S. Cenini, F. Ragaini, Catalytic Reductive Carbonylation of Organic Nitro Compounds, Chap. 4, Kluwer Academic Press, Dordrecht, 1997, and references therein.
[8] G. Fachinetti, T. Funaioli, P.F. Zanazzi, J. Organomet. Chem. 460 (1993) C34.
[9] F. Ragaini, S. Cenini, A. Fumagalli, C. Crotti, J. Organomet. Chem. 428 (1992) 401.
[10] F. Ragaini, S. Cenini, F. Demartin, Organometallics 13 (1994) 1178.
[11] F. Ragaini, P. Sportiello, S. Cenini, J. Organomet. Chem., in press.
[12] L. Garlaschelli, R. Della Pergola, S. Martinengo, Inorg. Synth. 28 (1990) 211.
[13] H.A. Tayim, A. Bouloukian, F. Awad, J. Inorg. Nucl. Chem. 32 (1970) 3799.