ELSEVIER

Journal of Molecular Catalysis A: Chemical 152 (2000) 47–54

JOURNAL OF MOLECULAR CATALYSIS A: CHEMICAL

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The unprecedented detection of the intermediate formation of *N*-hydroxy derivatives during the carbonylation of 2′-nitrochalcones and 2-nitrostyrenes catalysed by palladium

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Received 27 February 1999; accepted 21 June 1999

Abstract

The carbonylation of 2′-nitrochalcones (**1**) in tetrahydrofuran, catalysed by $Pd(TMB)_2$ (TMBH = 2,4,6-trimethylbenzoic acid) at 30 atm of carbon monoxide and 170°C, gave the corresponding quinolones (**2**), together with the *N*-hydroxyquinolones (**3**). In some cases the latter become the most abundant products. Similar reactions have been observed in the carbonylation of 2-nitrostyrenes (**4**) with the same catalytic system but in the presence of TMPhen (3,4,7,8-tetramethyl-1,10-phenanthroline), which gave the corresponding indoles (**5**), together with the *N*-hydroxyindoles (**6**). This is the first case where the formation of *N*-hydroxy derivatives has been observed during the catalytic carbonylation of organic nitro compounds. The use of Pd/C without any additive as catalyst has also been investigated.

Keywords: Organic nitro compounds; Catalytic carbonylation; Heterocycles; *N*-Hydroxy derivatives; Palladium

1. Introduction

The catalytic carbonylation of organic nitro compounds has been recently deeply investigated by several research groups, both from industries and universities [1]. The main objective was to find a new catalytic synthesis of important chemicals such as isocyanates, carbamates and ureas, avoiding the use of the dangerous and corrosive phosgene. However, this methodology has also been applied with success to the synthesis of heterocycles, by carbonylation of aromatic nitro compounds bearing in the *ortho* position an unsaturated group, able to intercept the presumed, intermediate nitrene species, formed by deoxygenation of the nitro group by carbon monoxide. [1] Very recently, the synthesis of indoles by carbonylation in particularly mild conditions of *ortho*-nitrostyrenes catalysed by palladium–phosphine derivatives, has been reported [2]. More drastic conditions were previously used by us in the same reaction, by using $Pd(TMB)_2$/TMPhen in toluene as catalyst (TMBH = 2,4,6-trimethylbenzoic acid; TMPhen = 3,4,7,8-tetramethyl-1,10-phenanthroline) [3]. However, in the latter case a much shorter reaction time was necessary, and usually better selectivities in indoles were

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[1] See Chap. 5 of Ref. [1].

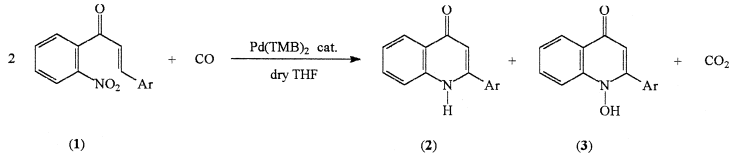
1381-1169/00/$ - see front matter
PII: S1381-1169(99)00267-8

achieved. We have also previously shown that the carbonylation of 2′-nitrochalcones catalysed by $Pd(TMB)_2$/TMPhen in toluene gives the reductive *N*-heterocyclization, allowing the one pot synthesis of 2-aryl-4-quinolones [4].

We report here that the carbonylation of 2-nitrostyrenes and 2′-nitrochalcones catalysed by $Pd(TMB)_2$ at 30 atm of carbon monoxide and 170°C in tetrahydrofuran, gives the indoles (in the presence of TMPhen) and the 4-quinolones (in the absence of added ligands), respectively, together with the corresponding *N*-hydroxy derivatives. In some cases the latter become the most abundant products, and this is the first case where the formation of *N*-hydroxy derivatives has been observed during the catalytic carbonylation of organic nitro compounds.

2. Results

The carbonylation of 2′-nitrochalcones (**1**) in dry tetrahydrofuran, catalysed by $Pd(TMB)_2$ at 30 atm of carbon monoxide and 170°C, for three h, gave the corresponding quinolones (**2**) together with the *N*-hydroxyquinolones (**3**) (Eq. (1)) (Table 1):

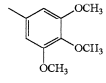
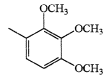
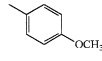
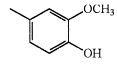


(**1**) (**2**) (**3**)

(1)

At the end of the catalytic reactions, a black precipitate (probably palladium metal) has always been

Table 1
Carbonylation of 2′-nitrochalcones (**1**) catalysed by $Pd(TMB)_2$ in THF[a,b]

Entry	(**1**) Ar	conversion (%)	(**2**) sel. (%)[c]	(**3**) sel. (%)[c]
a		100	44.9	55.1
b		100	60.8	39.2
c		100	24.3	75.7
d		73	42.0	25.0
e		63	40.0	18.5
f		100	47.0	53.0
g		100	68.1	31.9

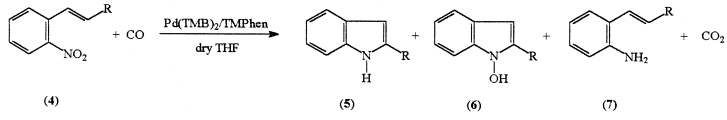
[a] Reactions carried out for 3 h at 170°C and 30 atm of carbon monoxide; TMBH = 2,4,6-trimethylbenzoic acid.
[b] Molar ratio substrate/Pd = 20; substrate = 0.25 mmol; solvent = dry THF (20 ml).
[c] Determined by ^{1}H NMR.

observed. Compounds (**3**) are formed in substantial amounts and in three cases (Entries **a**, **c** and **f**, Table 1) they represent the most abundant products of the reaction.

The solvent used in the catalytic reactions (THF) plays a fundamental role. The same catalytic reaction carried out in toluene in the presence of TMPhen as ligand of $Pd(TMB)_2$, gave norgraveoline (Ar=3,4-OCH_2O–C_6H_3; 78% isolated yield) together with the corresponding 2,3-dihydroderivative (16%), with no evidence for the formation of *N*-hydroxy derivatives [4]. Moreover, when the same catalytic reaction was carried out in the presence of TMPhen (molar ratio ligand/palladium = 2), but in THF instead of toluene as solvent, only the *N*-hydroxy derivative could be isolated from the reaction mixture (Ar=C_6H_5, 52% conversion, 28% of (**3**); Ar=3-OCH_3–4-OH–C_6H_3, 100% conversion, 66.5% of (**3**)).

However, the outcome of the reaction appears to depend from a delicate balance between the steric and electronic effects of the added ligands and the nature of the substrates. By using DPPE (1,2-bis-diphenylphosphinoethane) as ligand, the reaction gave nearly the same result of the one carried out in the absence of ligands (Ar=3-OCH_3–4-OH–C_6H_3), while for Ar=C_6H_5, a 42% conversion was observed, with formation of 25% of (**3**), compound (**2**) being not formed.

When Ar–BIAN (bis (*para*-methylphenylimino acenaphtene)) [2] was used as ligand, no substantial differences were observed from those reported in Table 1 (Entries **a**, **b** and **g**, Table 1). Finally, by using Pd/C as catalyst we observed for Ar=C_6H_5 a 31% conversion, with formation of (**3**) (23%) while no compound (**2**) was detected among the products, and for Ar=3-OCH_3-4-OH–C_6H_3, a 100% conversion gave 62% of (**2**) and 38% of (**3**).



(2)

Analogous reactions to those above described, have been carried out on *ortho*-nitrostyrenes derivatives (**4**) (Eq. (2)) (Table 2):

At the end of the reactions, decomposition of the catalyst was observed.

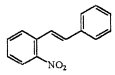
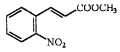
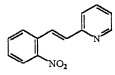
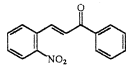
Even in this case the formation of indoles (**5**) is accompanied by the formation of the corresponding *N*-hydroxy derivatives (**6**), with the exception of the reaction on β-benzoyl–*ortho*-nitrostyrene (Entry **d**, Table 2) (in this latter case 6.8% of 2-phenylquinoline was also obtained). In the case of 2-[2-(2-nitrophenyl)ethenyl]pyridine (entry **c**, Table 2), the *N*-hydroxy derivative (**6**) was present in higher amount than the corresponding indole (**5**). In all the reactions, variable amounts of the corresponding amines (**7**) were detected in the final reaction mixtures. In one case (entry **a**, Table 2) the major product (42.7%) was the corresponding azo derivative. Reactions carried out on 2-[2-(2-nitrophenyl)ethenyl]pyridine, by using $Pd(TMB)_2$ without ligands or Pd/C as catalyst gave very poor conversions (8–10%) and no *N*-hydroxy derivative is obtained.

3. Conclusions

We have recently demonstrated that in the catalytic cyclization reactions carried on 2′-nitrochalcones and 2-nitrostyrenes the corresponding amines were not intermediately formed [5]. The open

[2] Note that in previous papers we used the name of DIAN-R for this class of ligands. However, since other groups are using the general name Ar-BIAN and this last terminology is of more general application, we have decided to adhere to this convention.

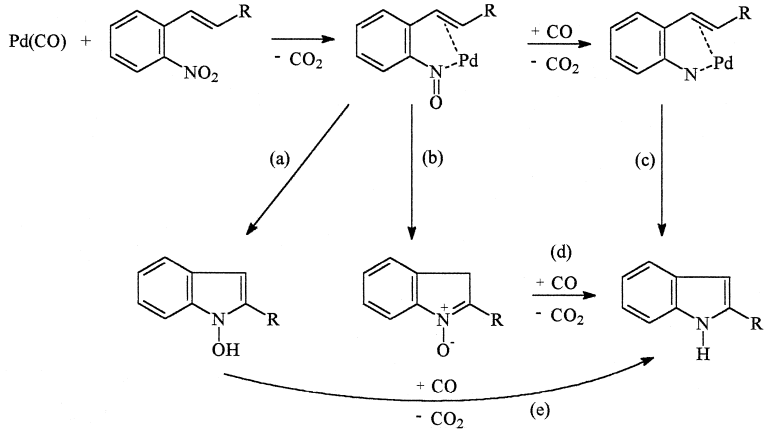
Table 2
Carbonylation of *ortho*-nitrostyrenes (**4**) catalysed by $Pd(TMB)_2$ /TMPhen in THF[a,b]

Entry	substrate (**4**)	conversion (%)	(**5**) sel. (%) [c]	(**6**) sel. (%) [c]	(**7**) sel. (%) [c]
a		89.7	23.2	14.0	3.9
b		100	65.2	25.6	9.2
c		100	28.8	38.2	4.7
d		97	58.4	-	25.1
e		100	68.4	-	12.3

[a] Reactions carried out for 3 h at 170°C and 30 atm of carbon monoxide; TMBH = 2,4,6-trimethylbenzoic acid, TMPhen = 3,4,7,8-tetramethyl-1,10-phenanthroline.
[b] Molar ratio substrate/Pd = 20; molar ratio ligand/catalyst = 2; substrate = 0.5 mmol; solvent = dry THF (20 ml).
[c] Determined by flash-chromatography on silica gel, and calculated with respect to converted nitrostyrene.

question remains related to the specie which attacks the double bond: a nitrene bound to the metal or a nitroso compound. The results here reported seem to suggest that both reaction pathways are possible, and that polar solvents such as THF favours the cyclization reaction from the intermediate nitroso compound before the subsequent deoxygenation to the nitrene species (path (a)) (Scheme 1):

However, another possibility exists. The intermediate nitroso derivative gives the nitrone before being deoxygenated (path (b)). Deoxygenation of the latter then leads to the final product (path (d)). This last reaction is expected to be very easy, since deoxygenation of the related trialkylamines–*N*-oxides and azoxyarenes by metal carbonyl complexes are well known reactions. This latter alternative



Scheme 1.

Table 3
Carbonylation of 2-[2-(2-nitrophenyl)ethenyl]pyridine catalysed by $Pd(TMB)_2$ /TMPhen in THF[a]

Entry	Conversion (%)	Time (h)	T (°C)	P (atm)	(**5**) sel. (%)[b]	(**6**) sel. (%) [b]	(**7**) sel. (%) [b]
a	100	6	170	30	68.6	–	7.3
b	100	3	170	30	28.8	38.2	4.7
c	37.5	1.5	170	30	24.8	59.6	7.1
d	100	5	130	30	38.4	54.9	3.9
e	100	4	130	30	31.7	57.2	6.2
f	100	3	130	30	29.3	62.7	5.6
g	100	4	130	20	28.7	56.3	4.2

[a] Molar ratio substrate/Pd = 20; molar ratio ligand/catalyst = 2; substrate = 0.5 mmol; solvent = dry THF (20 ml).
[b] Determined by flash chromatography and ^{1}H NMR with respect to converted nitrostyrene.

avoids the formation of the indole via a nitrene specie (path (c)). However, the formation of an imido intermediate would better explain the formation of the corresponding amine. Finally, we have demonstrated that the *N*-hydroxy derivative can be an intermediate in the synthesis of the indole, since preformed *N*-hydroxy derivative of 2-(2′-pyridil)indole under the catalytic conditions of Table 2 gives quantitatively the corresponding indole derivative. Thus, while path (a) + (e) is almost surely operating, we cannot still exclude that the reaction also occurs via path (c), since in this way the formation of the amines can be readily accounted for.

Similar arguments can be extended to the cyclization reactions carried out on 2′-nitrochalcones. Even in this case preformed *N*-hydroxy derivative of 2-benzo[1,3]dioxol-5-yl-1*H*-quinolin-4-one under the catalytic conditions of Table 1 gives quantitatively the corresponding *N–H* quinolone derivative.

It is interesting to note that the recently reported stoichiometric synthesis *N*-hydroxyindoles starting from *N*-hydroxy-2-oxindole [6] (the first efficient synthesis of these compounds), requires three steps. The catalytic synthesis here reported appears to be simpler and even the selectivity can be improved. In fact by using (**4c**) as starting material and reducing the reaction time to 1.5 h, the conversion of the styrene drastically decreases, but the selectivity in the *N*-hydroxy derivative rises from 38.2 to 59.6 (entries **b** and **c**, Table 3). For a longer reaction time (entry **a**), no *N*-hydroxy derivative is present in the reaction mixture, as expected. For other reactions carried out at 130°C we observed a slight improvement of the yields of the *N*-hydroxy derivative by decreasing the reaction time (entries **d**–**f**, Table 3), while a decrease of the reaction pressure practically has no effect (entries **e** and **g**).

4. Experimental section

All reactions are conducted under a CO atmosphere using an autoclave (see also later).

^{1}H NMR spectra were recorded on a Bruker WP 80 SJ spectrometer and on a Brucker AC-200 (200 MHz) spectrometer with $SiMe_4$ as internal standard. MS were performed on a VG 7070 EQ.

Carbon monoxide was of high purity grade. THF was dried by standard procedures, degassed and stored under dinitrogen before use.

Literature methods were used for the preparation of $Pd(O_2CR)_2$ [7,8] and for Ar-BIAN [9,10]; DPPE was furnished by Fluka, TMPhen and Pd/C were supplied by Aldrich.

2′-Nitrochalcones were obtained in high yields from ArCHO and 2-nitroacetophenone according to a modified procedure [11]. Literature methods were used for the preparation of 2-[2-(2-nitrophenyl)ethenyl]pyridine [12], 2-nitrostilbene, the methyl ester of (2-nitrophenyl)-2-propenoic acid [13] and 3-(2-nitrophenyl)-1-phenyl-2-propen-1-one [14].

4.1. Catalytic reactions

The reactions under high pressure were conducted in a glass liner inside a 200-ml stainless steel autoclave. The air in the autoclave was replaced with dinitrogen by three freeze–pump–thaw cycles, before the introduction of carbon monoxide at the required pressure. The autoclave was heated by a thermoregulated silicone oil bath and magnetic stirring was applied. At the end of the reaction the autoclave was rapidly cooled in an ice bath and then blown off. Selectivities were calculated from the amount of the starting material reacted. Products of the reactions were separated by flash chromatography. For the conditions of the cyclization reactions see Tables 1–3.

4.2. Identification of organic compounds

4.2.1. ***Compound (2a)***
^{1}H NMR (δ in DMSO ppm): 11.52 (s, 1H), 7.72 (s, 1H), 7.61 (dt, 1H), 7.42 (d, 1H), 7.30 (dt, 1H), 7.12 (d, 1H) 7.01 (dd, 1H), 6.30 (s, 1H), 6.11 (s, 2H); MS (m/z, CI): 266 (M).

4.2.2. ***Compound (2b)***
^{1}H NMR (δ in DMSO ppm): 11.71 (s, 1H), 8.11 (dd, 1H), 7.4–7.8 (m, 7H), 7.31 (d, 1H), 6.36 (s, 1H), MS (m/z, CI): 238 (M + 1).

4.2.3. ***Compound (2c)***
^{1}H NMR (δ in DMSO ppm): 11.28 (s, 1H), 8.12 (dd, 1H), 7.1–7.6 (m, 7H), 6.19 (s, 1H), 3.91 (s, 6H), 3.77 (s, 3H); MS (m/z, CI): 312 (M + 1).

4.2.4. ***Compound (2d)***
^{1}H NMR (δ in DMSO ppm): 11.32 (s, 1H), 8.10 (dd, 1H), 7.2–7.8 (m, 5H), 6.19 (s, 1H), 3.84 (s, 3H), 3.77 (s, 3H), 3.73 (s, 3H); MS (m/z, CI): 312.

4.2.5. ***Compound (2e)***
^{1}H NMR (δ in DMSO ppm): 11.28 (s, 1H), 8.07 (dd, 1H), 7.1–7.5 (m, 7H), 6.15 (s, 1H), 3.83 (s, 3H); MS (m/z, CI): 252 (M + 1).

4.2.6. ***Compound (2f)***
^{1}H NMR (δ in DMSO ppm): 10.98 (s, 1H), 8.12 (dd, 1H), 7.3–7.8 (m, 7H), 6.12 (s, 1H); MS (m/z, CI): 258 (M + 3) 255 (M + 1).

4.2.7. ***Compound (2g)***
^{1}H NMR (δ in DMSO ppm): 11.27 (s, 1H), 8.11 (dd, 1H), 7.0–7.5 (m, 7H), 6.10 (s, 1H), 3.79 (s, 3H), 3.31 (s, 1H); MS (m/z, CI): 268 (M + 1).

4.2.8. ***Compound (3a)***
^{1}H NMR (δ in DMSO ppm): 11.95 (s, 1H), 8.08 (s, 1H), 7.79 (dt, 1H), 7.61 (d,1H), 7.1–7.4 (m, 4H), 6.42 (s, 1H), 6.22 (s, 2H); MS (m/z, CI): 282 (M + 2).

4.2.9. ***Compound (3b)***
^{1}H NMR (δ in DMSO ppm): 10.00 (s, 1H), 8.07 (dd, 1H), 7.2–7.7 (m, 7H), 7.11 (d, 1H), 6.15 (s, 1H), MS (m/z, CI): 222 (M + 1).

4.2.10. ***Compound (3c)***
^{1}H NMR (δ in DMSO ppm): 11.72 (s, 1H), 8.17 (dd, 1H), 7.2–7.7 (m, 7H), 6.31 (s, 1H), 3.97 (s, 6H), 3.82 (s, 3H); MS (m/z, CI): 328 (M + 1).

4.2.11. ***Compound (3d)***
^{1}H NMR (δ in DMSO ppm): 11.61 (s, 1H), 8.17 (dd, 1H), 7.2–7.8 (m, 5H), 6.51 (s, 1H), 3.86 (s, 3H), 3.80 (s, 3H), 3.75 (s, 3H); MS (m/z, CI): 328.

4.2.12. ***Compound (3e)***
^{1}H NMR (δ in DMSO ppm): 11.51 (s, 1H), 8.12 (dd, 1H), 7.1–7.6 (m, 7H), 6.29 (s, 1H), 3.87 (s, 3H); MS (m/z, CI): 268 (M + 1).

4.2.13. ***Compound (3f)***
^{1}H NMR (δ in DMSO ppm): 11.18 (s, 1H), 8.18 (dd, 1H), 7.6–7.9 (m, 6H), 7.34 (m, 1H), 6.33 (s, 1H); MS (m/z, CI): 274 (M + 3) 272 (M + 1).

4.2.14. ***Compound (3g)***
^{1}H NMR (δ in DMSO ppm): 11. 87 (s, 1H), 8.20 (dd, 1H), 7.1–7.6 (m, 7H), 6.22 (s, 1H), 3.86 (s, 3H), 3.33 (s, 1H); MS (m/z, CI): 284 (M + 1).

4.2.15. ***Compound (5a)***
^{1}H NMR (δ in $CDCl_3$ ppm): 8.32 (s, 1H), 7.1–7.7 (m, 9H), 6.84 (s, 1H);, MS (m/z, CI): 194 (M + 1).

4.2.16. ***Compound (5b)***
^{1}H NMR (δ in $CDCl_3$ ppm): 8.91 (s, 1H), 7.72 (dd, 1H), 7.45 (dd, 1H) 7.32 (dd, 1H), 7.25 (dd, 1H), 7.17 (dd, 1H) 3.97 (s, 3H); MS (m/z, CI): 176 (M + 1).

4.2.17. ***Compound (5c)***
^{1}H NMR (δ in $CDCl_3$ ppm): 9.63 (s, 1H), 8.57 (d, 1H), 7.73 (m, 3H), 7.2–7.4 (m, 4H), 7.07 (s, 1H); MS (m/z, CI): 195 (M + 1).

4.2.18. ***Compound (5d)***
^{1}H NMR (δ in $CDCl_3$ ppm): 9.29 (s, 1H), 8.01 (d, 1H), 7.3–7.7 (m, 9H), 7.18 (m, 1H); MS (m/z, CI): 222 (M + 1); *CHN*: calc. C 81.43%, H 5.01%, N 6.21, exp. C 81.31%, H 5.04%, N 6.21%.

4.2.19. ***Compound (6a)***
^{1}H NMR (δ in $CDCl_3$ ppm): 9.28 (s, 1H), 7.2–7.7 (m, 9H), 7.02 (s, 1H); MS (m/z, CI): 210 (M + 1).

4.2.20. ***Compound (6b)***

^{1}H NMR (δ in $CDCl_3$ ppm): 10.21 (s, 1H), 7.66 (dd, 1H), 7.56 (dd, 1H) 7.43 (dd, 1H), 7.36 (dd, 1H), 7.25 (dd, 1H) 4.01 (s, 3H); MS (m/z, CI): 192 (M + 1).

4.2.21. ***Compound (6c)***

^{1}H NMR (δ in $CDCl_3$ ppm): 11.20 (s, 1H), 8.52 (d, 1H), 7.85 (d, 2H), 7.61 (dd, 2H), 7.27 (m, 2H), 7.11 (m, 1H), 6.91 (s, 1H); MS (m/z, CI): 211 (M + 1).

Acknowledgements

We thank MURST ex 40% for financial support.

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