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Intramolecular amination catalysed by ruthenium and palladium. Synthesis of 2-acyl indoles and 2-aryl quinolines by carbonylation of 2-nitrochalcones

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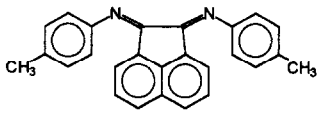
Abstract

The carbonylation in toluene of 2-nitrochalcones at 20 bar and 100°C, with $Pd(TMB)_2$ as catalyst and TMPhen as cocatalyst (TMBH = 2,4,6-trimethyl benzoic acid; TMPhen = 3,4,7,8-tetramethyl-1,10-phenanthroline) gave the corresponding 2-acyl indoles in 60–98% yields. The use as catalyst of $Ru_3(CO)_{12}$ activated by a rigid α-diimine ligand such as DIAN–Me(*), in ethanol–water, at 30 bar and 170°C, gave a mixture of the corresponding acyl indoles and quinolines, the latter being usually the most abundant products.

Keywords: Amination; Carbonylation; Palladium; Ruthenium; 2-Acyl indoles; 2-Arylquinolines

1. Introduction

We recently reported on the carbonylation of 2′-nitrochalcones to give 2-aryl-substituted-4-quinolines, catalysed by $Ru_3(CO)_{12}$ in the presence of DIAN–Me



(*) DIAN-Me

as ligand [1] and by the system $Pd(TMB)_2$ /TMPhen (TMBH = 2,4,6-trimethyl benzoic acid; TMPhen = 3,4,7,8-tetramethyl-1,10-phenanthroline) [2]. The palladium catalyst has also been used in the catalytic carbonylation of *o*-nitrostyrenes, obtaining the corresponding indoles with a selectivity generally ranging from 70 to 100% [3]. The synthesis of indoles by carbonylation of *o*-nitrostyrenes, is also catalysed by $Pd(PPh_3)_2Cl_2/SnCl_2$ [4] and by metal carbonyls such as $Fe(CO)_5$, $Ru_3(CO)_{12}$ and $Rh_6(CO)_{16}$ [5].

We report here on the catalytic carbonylation of 2-nitrochalcones (**1a–1m**) by using the catalysts previously used in the case of 2′-nitrochalcones as substrates.

From these reactions, 2-acyl indoles (**2a–2m**) (palladium catalyst) have been obtained with high selectivity, while with the ruthenium catalyst a mixture of 2-acyl indoles (**2a–2m**) and quinolines (**3a–3m**) has been obtained.

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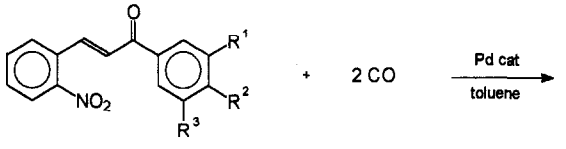
2. Results

2.1. Carbonylation of 2-nitrochalcones (1a–1m). Palladium as catalyst.

By carbonylation of 2-nitrochalcones (**1a–1m**) in toluene, at 20 bar and 100°C, with $Pd(TMB)_2$/TMPhen as catalyst, the corresponding 2-acylindoles (**2a–2m**) have been obtained (Eq. 1) (Table 1):



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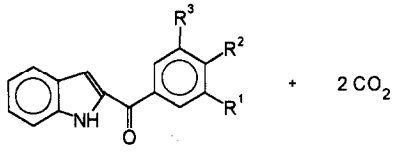

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Although the reaction conditions are rather mild, good conversions were achieved and a high selectivity in 2-acyl indoles (60–98%) is observed.

By-products of these reactions are the amines corresponding to the starting materials.

Dry toluene was a good solvent, while some reactions carried out by using tetrahydrofuran as solvent gave poor yields (ca. 20%) of the indoles ($R^1 = R^3 = H$; R^2 = Me, OMe; $R^1 = R^2$ = Me, $R^3 = H$).

Electron donating substituents on the phenyl ring of the acyl residue (OMe, Me) seem to favour the selectivity of the reaction.

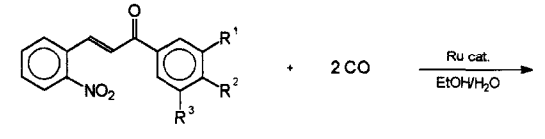
On the other hand the formation of amines as by-products, which is rather common in the catalytic reductive carbonylation of organic nitro compounds, might suggest the intermediate formation of nitrene species, which can abstract hydrogen from the solvent (or from adventitious moisture) before the ring closure to give the indole nucleus.

Electron withdrawing substituents on the phenyl ring of the acyl residue could favour indirectly the hydrogen abstraction slowing down the ring closure.

We finally point out that in these reactions we never observed the formation of six membered rings such as quinolines, which are the most abundant products when ruthenium is used as catalyst (see Section 2.2)

2.2. Carbonylation of 2-nitrochalcones (1a–1m). Ruthenium as catalyst

By carbonylation of 2-nitrochalcones (**1a–1m**) in ethanol/water, at 30 bar and 170°C with $Ru_3(CO)_{12}$/DIAN–Me as catalyst, a mixture of the corresponding quinolines (**3a–3m**) and 2-acyl indoles (**2a–2m**) has been obtained (Eq. 2) (Table 2).



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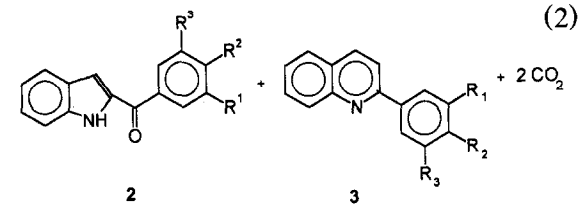

2 3

We have previously shown that the $Ru_3(CO)_{12}$/DIAN–Me catalytic system is a very efficient catalyst for the reduction with CO/H_2O of nitrobenzene to aniline [6].

It seems thus reasonable to suppose that while the 2-acyl indoles are formed via the intermediate formation of nitrene species, quinolines are formed via the intermediate formation of the corresponding amines.

Although we never observed the presence of amines in the reaction medium, it could be that in a polar solvent like ethanol the ring closure to give the quinolines rapidly takes place [7]. Nucleophilic attack of the amine on the carbonyl group of the acyl residue, should be favoured by electron withdrawing substituents on the phenyl ring, while the highest yield of quinoline (92%) has been observed with a substituent such as a methyl group (Table 2, compound **3b**). This effect might be due to the presence in solution of the transition metal catalyst, to which the intermediate 2-aminochalcones should be bound.

Probably, a common intermediate is formed during the catalytic reactions, that is the corresponding nitrene species. This intermediate can evolve to give the corresponding amine, or it can attack in concurrent ways the double bond or the carbonyl function, leading to the formation of 2-acylindoles (**2a–2m**) and quinolines (**3a–3m**) respectively.

The formation of quinolines by this route, is similar to the reaction scheme proposed for the synthesis of Schiff bases from organic nitro derivatives and aldehydes, catalysed by $Rh_6(CO)_{16}$ in pyridine [8].

Analogous intramolecular cyclisation reactions can be considered the catalytic carbonylation of 2-nitrobenzaldiformamides to yield quinazoline derivatives [9] and the catalytic carbonylation of *N*-(2-nitrobenzoyl)amides to yield 4(3*H*)-quinozalinone derivatives [10].

It is worth mentioning also that compounds similar to 2-nitrochalcones prepared in situ from *o*-nitrobenzaldehyde and carbonyl compounds such as acetaldehyde, acetone or acetophenone can be reduced by a stoichiometric amount of tetracarbonylhydridoferrate anion to the corresponding quinolines [11]

Table 1
Carbonylation of 2-nitrochalcones (**1a–1m**) catalysed by $Pd(TMB)_2$ /TMPhen [a]

2-Nitrochalcones (1)	R^1	R^2	R^3	Conversion (%)	2-Acyl indole (2) (%) [b]
a [13]	H	OMe	H	100	98 [16]
b [c] [12]	H	Me	H	100	98 [16]
c [12]	H	H	H	90	67 [16]
d [12]	H	Br	H	100	62
e [14]	H	Cl	H	90	76 [16]
f [15]	H	F	H	100	60 [17]
g [12]	H	CN	H	100	66
h [12]	OMe	OMe	H	90	83 [16]
i [12]	Me	Me	H	100	96
l	Cl	Cl	H	90	65
m	OMe	OMe	OMe	100	98

[a] T = 100°C; p_{CO} = 20 bar; TMPhen/$Pd(TMB)_2$ = 2; substrate/$Pd(TMB)_2$ = 20; [substrate] = 5×10^{-4} mol; solvent = toluene (20 ml); t = 2 h; TMBH = 2,4,6-trimethyl benzoic acid; TMPhen = 3,4,7,8-tetramethyl-1,10-phenanthroline.
[b] Isolated by flash chromatography.
[c] T = 180°C and p_{CO} = 60 bar were used.

Table 2
Carbonylation of 2-nitrochalcones (**1a–1m**) catalysed by $Ru_3(CO)_{12}$ /DIAN–Me [a,b]

2-Nitrochalcone (1)	R^1	R^2	R^3	Quinoline (3) (%) [c]	2-Acyl indole (2) (%) [c]
a	H	OMe	H	61 [18]	39
b	H	Me	H	92 [18]	8
c	H	H	H	57 [18]	43
d	H	Br	H	52 [19]	48
e	H	Cl	H	53 [19]	47
f	H	F	H	78 [20]	22
g	H	CN	H	56	44
h	OMe	OMe	H	66 [21]	34
i	Me	Me	H	46 [22]	54
l	Cl	Cl	H	75 [22]	25
m	OMe	OMe	OMe	85 [22]	15

[a] T = 170°C; p_{CO} = 30 bar; DIAN–Me/$Ru_3(CO)_{12}$ = 3; substrate/$Ru_3(CO)_{12}$ = 100; [substrate] = 5×10^{-4} mol; solvent = ethanol/water (20 ml + 5 ml); t = 3 h.
[b] The conversion is always 100%.
[c] Determined by NMR.

3. Conclusions

The number of heterocycles which can be catalytically obtained by carbonylation of aromatic nitro compounds bearing in the ortho position a substituent able to intercept the presumed intermediate nitrene species, is rapidly growing [1–5,9,10].

We have reported here the application of two catalytic systems to the synthesis of 2-acyl indoles and quinolines from very readily available starting compounds. The mechanistic aspects of these reactions require however further investigations in order to be clarified.

4. Experimental

IR spectra were recorded on Perkin Elmer 1310 and Nicolet MX-1FT-IR spectrophotometers. ^{1}H NMR spectra were recorded on a Bruker WP 80 SJ spectrometer with $SiMe_4$ as internal standard. MS was performed on a VG 7070 EQ. Carbon monoxide was of high purity grade. Solvents were distilled before use; literature methods were used for the preparation of various 2-nitrochalcones [12].

The reactions under high pressure were conducted in a glass liner inside a 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 desired pressure. The autoclave was placed in a thermoregulated silicone oil bath and magnetic stirring was applied. At the end of the reactions, 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 cyclisation reactions see Tables 1 and 2.

4.1. Identification of organic compounds

*4.1.1. Compound (**1l**)*

m.p. 210–212°C (from ethanol), Calc. (Found) (%): C 56.07 (55.99), H 2.08 (2.1), N 4.36 (4.2). ^{1}H-NMR ($CDCl_3$, ppm); 8.2 (d, $J = 18.6$ Hz; 1H), 7.8–7.5 (m, 6H), 7.8 (d, $J = 18.6$ Hz; 1H), 7.28 (s, 1H).

*4.1.2. Compound (**1m**)*

m.p 148–150°C (from ethanol), Calc. (Found) (%): C 62.97 (62.31), H 4.95 (5.1), N 4.08 (4.11). ^{1}H-NMR ($CDCl_3$, ppm); 8.8–8.5 (m, 6H), 8.17 (d, $J = 17.3$ Hz; 1H), 8.0 (d, $J = 17.3$ Hz; 1H), 3.9 (s, 9H)

*4.1.3. Compound (**2d**)*

^{1}H NMR ($CDCl_3$, ppm): 12.2 (s, 1H), 8.12 (d, $J = 7.8$ Hz, 2H), 7.62–7.01 (m, 5H), 7.4 (d, $J = 7.8$, 2H); MS (m/z, EI, 70 eV): 301 (M^+ 54%), 299 (53%), 144 (26%), 116 (100%); IR (cm^{-1}, in Nujol): 3285, 1625.

*4.1.4. Compound (**2g**)*

^{1}H NMR ($CDCl_3$, ppm); 12.07 (s, 1H), 7.75 (d, $J = 8.4$ Hz, 2H), 8.05–7.13 (m, 5H), 7.45 (d, $J = 8.4$, 2H); MS (m/z, EI, 70 eV): 246 (M^+ 100%), 220 (13%), 144 (36%), 116 (38%); IR (cm^{-1}, in Nujol): 3287, 2218, 1627.

*4.1.5. Compound (**2i**)*

^{1}H NMR ($CDCl_3$, ppm); 11.9 (s, 1H), 7.8–7.11 (m, 8H), 2.3 (s,6H); MS (m/z, EI, 70 eV): 249 (M^+ 100%), 144 (21%), 116 (76%); IR (cm^{-1}, in Nujol): 3290, 1625.

*4.1.6. Compound (**2l**)*

^{1}H NMR ($CDCl_3$, ppm); 12.9 (s, 1H), 7.9–7.2 (m, 8H); MS (m/z, EI, 70 eV): 293 (M^+ 6%), 291 (22%), 289 (17%), 144 (30%), 116 (100%); IR (cm^{-1}, in Nujol): 3289, 1630.

*4.1.7. Compound (**2m**)*

^{1}H NMR ($CDCl_3$, ppm); 11.87 (s, 1H), 8.1–7.55 (m, 5H), 7.25 (s, 2H), 3.9 (s, 9H); MS (m/z, EI, 70 eV): 311 (M^+ 34%), 144 (24%), 116 (100%); IR (cm^{-1}, in Nujol): 3287, 1628.

*4.1.8. Compound (**3g**)*

^{1}H NMR ($CDCl_3$, ppm); 8.05 (d, $J = 8.2$ Hz, 1H), 7.25(d, $J = 8.2$ Hz, 1H), 7.8–7.0 (m, 8H); MS (m/z, EI, 70 eV): 230 (M^+ 100), 203 (15%), 128 (30%); IR (cm^{-1}, in Nujol): 2220.

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