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4(1*H*)-QUINOLINONE ALKALOIDS. AN EFFICIENT SYNTHESIS OF GRAVEOLINE BY PALLADIUM-CATALYSED REDUCTIVE *N*-HETEROCYCLISATION.

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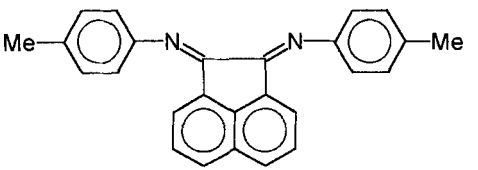
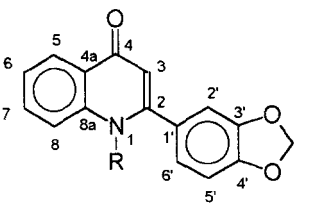
Abstract. An efficient synthesis of the 4*H*-quinolone alkaloid graveoline has been achieved by a route featuring an Pd(II)-catalysed reductive *N*-heterocyclisation [CO(3 MPa), $Pd(TMB)_2$, TMPhen, 170 °C, 3h] of 2'-nitrochalcone as a key step.

4(1*H*)-Quinolinones (4-quinolones) possess a very broad range of biological activity and several of them are currently used as medicinal agents.[1] Synthetic routes to these compounds frequently involve multistep approaches based on the thermal cyclisation of acrylates arising from the reaction of amines with β-ketoesters (Conrad-Limpach reaction).[2] In contrast, 2-arylsubstituted 4-quinolones are difficult to synthesize by this procedure. Some of us have previously reported that $Ru_3(CO)_{12}$ in the presence of bis(*p*-tolyl-imino)acenaphthene (DIAN-Me) **1** is an efficient catalyst in the reductive *N*-

heterocyclisation of 2'-nitrochalcones under CO pressure, allowing the one-pot synthesis of 2-aryl-4-quinolones.[3,4] To the best of our knowledge, there are only two precedents on the metal-assisted cyclisation to 2-aryl-4-quinolones.[5,6] In this paper we describe the optimisation of our methodology to prepare graveoline **2**, a long-known alkaloid embodying the 4(1*H*)-quinolinone moiety.[7] The starting material in our synthesis was chalcone **3** which was conveniently prepared by aldol condensation of 2-nitroacetophenone with piperonal. When **3** was reacted under 3 MPa of carbon monoxide at 170 °C for 3 h in the presence of DIAN-Me (3×10^{-2} equiv) and a catalytic amount of $Ru_3(CO)_{12}$ (10^{-2} equiv) in EtOH-H_2O , the corresponding 2,3-dihydroderivative **5** was obtained as a major product in 57% yield together with 38% yield of norgraveoline **4** (entry 1, Table).

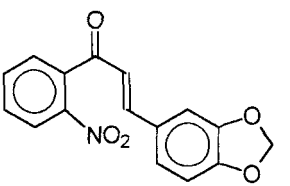


1

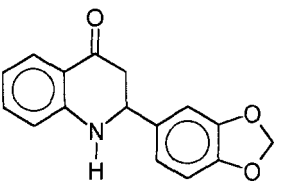


2 R = Me

4 R = H



3



5

Although this catalytic system is highly chemoselective (*i.e.*, reduction of the carbonyl or of conjugated double bond was not observed), changing the ratio of nitrogen bidendate ligand to $Ru_3(CO)_{12}$ for **3** did not markedly affect this unsatisfactory product distribution. Accordingly, the catalytic activity of some Pd-complexes was then examined. The results are summarised in the Table.

Table. Catalytic activities of transition-metal complexes for the reductive *N*-heterocyclisation of compound 3.

Entry	*Catalyst (mmol)*	*Additive (mmol)*	*Conv (%)*	*Isolated yield (%)*	
				4	**5**
1 [a]	$Ru_3(CO)_{12}$ (2.47×10^{-2})	DIAN-Me (7.41×10^{-2})	100	38	57
2 [b]	$Pd(TMB)_2$ (2.5×10^{-2})	TMPhen (5×10^{-2})	100	78	16
3 [b]	$Pd(TMB)_2$ (2.5×10^{-2})	TMPhen (5×10^{-2}) TMBH (0.5)	100	74	21
4 [b]	$Pd(PhCN)_2Cl_2$ (2.5×10^{-2})	-	51	26	22
5 [b]	$Pd(PhCN)_2Cl_2$ (2.5×10^{-2})	TMPhen (5×10^{-2})	32	20	10

[a] 2'-nitrochalcone (2.47 mmol) in EtOH (47 mL) - H_2O (3 mL) under CO (3 MPa) at 170°C for 3 h.

[b] 2'-nitrochalcone (2.5 mmol) in toluene (50 mL) under CO(3 MPa) at 170°C for 3 h.

Among them, palladium bis(2,4,6-trimethyl benzoate) $Pd(TMB)_2$ in the presence of 3,4,7,8-tetramethyl-1,10-phenanthroline (TMPhen) as a ligand and 2,4,6-trimethylbenzoic acid (TMBH) as cocatalyst,[8] showed high activity and addition of 2-fold amount of TMPhen to that of Pd atom in toluene (170°C ; 3 MPa CO; 3 h) gave the best result (entry 2) with the maximum selectivity for **4**. The presence of free TMBH was not necessary to obtain good selectivities(entry 3). On the other hand, the use of $Pd(PhCN)_2Cl_2$ in place of $Pd(TMB)_2$ under the same conditions, decreased both the yield and the selectivity (entry 4), whereas

the presence of TMPhen lowered the yield of **5** with little change in the selectivity (entry 5).

These results suggest that chemoselectivity is controlled by a Pd-phenanthroline complex formed *in situ*, a well established catalyst, very active and selective for the synthesis of isocyanates, carbamates and nitrogen-containing heterocycles by carbonylation of organic nitrocompounds.[8] The formation of quinolone **4** can be understood by assuming the generation of an active nitrene intermediate which can insert into C-H bond and a similar reaction pathway was proposed in previously reported reductive coupling and carbonylation of nitroarenes catalysed by palladium complexes.[9]

Alternatively, we felt that this sequence could be improved by obviating the separation of **5** from **4**. Thus, the mixture arising from entry *2* was directly dehydrogenated with 1.1 equiv (*vs* **5**) of DDQ (2,3-dichloro-5,6-dicyano-1,4-benzoquinone) in toluene at 60°C for 2 h to give norgraveoline **4** as the sole product in nearly quantitative yield.[10] With the requisite **4** in hand, introduction of the Me group at position 1 was readily accomplished with MeI in refluxing acetone in the presence of K_2CO_3.

In conclusion, the present procedure allows expeditious acquisition of graveoline **2** in 71% overall yield in four steps from commercially available 2-nitroacetophenone with employing any tedious sequence and it should provide a valuable alternative to the well-known basic approach.

Experimental section

2'-nitrochalcone **3** was obtained in 85% yield from piperonal and 2-nitroacetophenone according to a modified procedure[11] ; yellow needles, m.p. 128-30 °C (EtOH) ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.0 (2H,s), 6.89 (1H,d, J = 7) , 6.91 (1H, dd, J = 8), 7.06 (1H, d, J = 2), 6.85 (A part of AB system,1H,d, J = 15) ,7.21 (B part of AB system, 1H,d, J = 15) ,7.71 (2H,m),8.11 (1H, dd, J = 8), 8.2 (1H, dd, J = 8).

Pd(II)-promoted reductive N-heterocyclisation of **3** (Entry 2). $Pd(TMB)_2$ (10.8 mg, 2.5 x 10^{-2} mmol) and TMPhen (11.8 mg, 5 10^{-2} mmol) were added to a solution of 2'-nitrochalcone **3** (802 mg, 2.5 mmol) in toluene (50 ml). The mixture was introduced into a glass liner inside a stainless steel autoclave previously purged with nitrogen and then evacuated. The autoclave was pressurized to 3 MPa with CO at room temperature and then heated to 170 °C (silicone oil bath). After 3 h the autoclave was cooled to room temperature and then slowly depressurized. Some metallic black Pd was deposited in the glass liner surface. The content of the vessel was transferred to a flask; the vessel was rinsed with two 50 mL portions of CH_2Cl_2 and resulting solution was filtered through a Celite pad, dried over $MgSO_4$, filtered and freed of solvent under reduced pressure. The residue dark orange solid was dissolved in a small amount of CH_2Cl_2-MeOH (19:1) and chromatographed on silica gel with the same solvent to afford sequentially dihydroderivative **5** (110 mg, 16%) and norgraveoline **4** (560 mg,78%) as pale yellow solids.

*3,4-Dihydro-2-(1,3-benzodioxol-5-yl)-4(1*H*)-quinolinone* **5** :m.p. 118-19 °C (EtOH) [Lit. [11]: 120-21°C] ^{1}H NMR (300 MHz; $CDCl_3$) δ 2.60 (A part of ABX system, 1H, *J* 16, 4.2; H-3_A); 2.83 (B part of ABX system, 1H, *J* = 16, 12; H-3_B), 4.67 (X part of ABX system, 1H, *J* = 12, 4.3; H-2); 6.01 (2H, s, OCH_2O); 6.63(1H, dd, *J* = 8.2 , H-6); 6.87 (1H, dd, *J* = 8.2, H-8); 6.90 (1H, d, *J* = 7, H-5'); 6.94 (1H, dd, *J* = 8.3, H-6'); 7.05 (1H, br s , NH); 7.08 (1H, d, *J* = 2, H-2'); 7.31 (1H, dt, *J* = 8.2, H-7); 7.60 (1H, dd, *J* = 8.2, H-5); ^{13}C NMR (75 MHz, $CDCl_3$,) δ 56.2 (C-2),45.3 (C-3), 192.5 (C-4), 117.6 (C-4a), 126.3 (C-5), 116.4 (C-6), 135.0 (C-7), 116,2 (C-8), 152.3 (C-8a), 135.5 (C-1'), 107.3 (C-2'), 147.3 (C-3'), 146.7 (C-4'), 108.1 (C-5'), 120.1 (C-6'), 101.9 (OCH_2O)., EI-MS(70 eV) 267 ($M^{+\cdot}$, 75%), 250 (15) 146 (100), 120 (25) 89 (32). Anal. Calcd for $C_{16}H_{13}NO_3$ (267.09): C,71.89; H, 4.91; N, 5.24. Found: C, 71.25; H, 4.61; N,5.01.

*2(1,3-Benzodioxol-5-yl)-4(1*H*)-quinolinone* **4**: m.p. 289-91°C (EtOH) [Lit.[7b] : 290-91°C]; ^{1}H NMR (300 MHz; $CDCl_3$) δ 6.14 (2H, s, OCH_2O), 6.31 (1H, s, H-3), 7.04 (1H, dd, *J* = 8.2; H-6'), 7.12 (1H, d, *J* = 8; H-5'), 7.32 (1H, dt, *J* = 8.2; H-6), 7. 43 (1H, d, *J* = 2 , H-2'), 7.65 (1H, dt, *J* = 8.2, H-8), 7.75 (1H, dd, *J* = 8.2; H-5),

11.55 (1H, br s, NH). ^{13}C NMR (75 MHz, $CDCl_3$): δ 199.6 (C-2), 106.7 (C-3), 176.4 (C-4), 121.6 (C-4a), 124.6 (C-5), 123.1 (C-6), 131.6 (C-7), 118.7 (C-8), 140.5 (C-8a), 107.5 (C-2'), 147.8 (C-3'), 149.1 (C-4'), 108.6 (C-5'), 121.8 (C-6'), 101.8 (OCH_2O). EI-MS (70 eV): 265 ($M^{+\cdot}$, 100%), 237 (42), 178 (20), 108 (12). Anal. Calcd for $C_{16}H_{11}NO_3$ (265.07); C,72.43; H,4.18; N, 5.28. Found: C,71.95; H, 4.09; N, 5.12.

Alternatively, the solution arising from filtration through a Celite pad (entry 2) was treated with DDQ (110 mg) and heated under stirring at 60°C until TLC [CH_2Cl_2-MeOH (19:1)] showed the disappearance of **5** (2 h). 2-Propanol (5 mL) was then added and stirring was continued for another hour. The reaction mixture was filtered and the greenish filtrate was evaporated to dryness. The residue was dissolved in CH_2Cl_2 and filtered again . The removal of solvent gave the crude norgraveoline **4** which was purified by chromatography on silica gel (CH_2Cl_2-MeOH 19:1) to give pure **4** (650 mg), m.p. 290-91 °C as colourless needles from EtOH.

2(1,3-Benzodioxol-5-yl)-1-methyl-4(1H)-quinolinone (graveoline) **2**. A mixture of **4** (50 mg, 0.18 mmol), anhydrous potassium carbonate (49.7 mg, 0.36 mmol) and MeI (15 μl, 0.27 mmol) in acetone (5 mL) was refluxed for 3 h. Filtration and removal of solvent *in vacuo* gave a yellowish solid which after chromatography on silica gel (EtOAc) afforded pure graveoline **2** (46 mg, 87%), m.p. 205-206 °C (acetone-hexane) [Lit.: [7b] 204-205 °C]; ^1H NMR (300 MHz, $CDCl_3$) δ 3.64 (3H, s, NMe), 6.05 (2H, s, OCH_2O), 6.29 (1H, s, H-3), 6.80 - 7.00 (2H, m), 7.20-8.00 (4H, m), 8.51 (1H,dd, J = 8.2, H-5). Anal. Calcd for $C_{17}H_{13}NO_3$ (279.09): C,73.09; H,4.69; N,5.02. Found: C,73.23; H,4.48; N,5.16.

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