Ruthenium Catalysed N-Heterocyclisation: Indoles from 2-Aminophenethyl Alcohols

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Dichlorotris(triphenylphosphine)ruthenium is highly active as a catalyst for the N-heterocyclisation of 2-aminophenethyl alcohols (2a—d) into indole derivatives in toluene under reflux, and the reactions proceed with spontaneous hydrogen evolution.

The Fischer synthesis[1] is widely used for construction of the indole skeleton, but there has been increasing interest recently in simpler and more direct methods for indole synthesis. One of the most promising routes, even from an industrial point of view, seems to be N-heterocyclisation of 2-aminophenethyl alcohols (2), since such compounds are easily derived from nitrotoluene derivatives (1) via condensation with formaldehyde[2] followed by reduction (Scheme 1).

However, the conversion of (2) into (3) has met with only limited success, severe conditions being necessary (250 °C
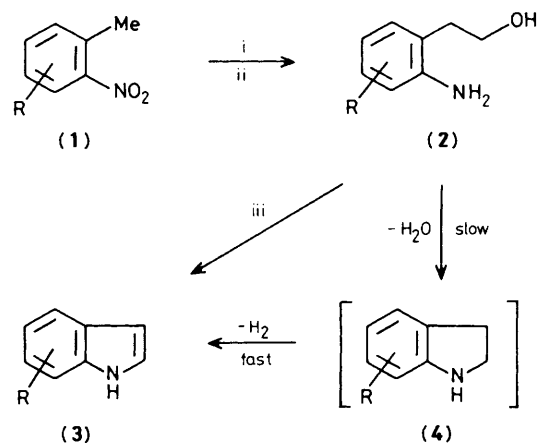
Scheme 1. *Reagents and conditions:* i, paraformaldehyde (0.5 equiv.), Triton B (0.02 equiv.), Me_2SO, 95 °C, 1 h; ii, Zn, $CaCl_2$, H_2O, reflux 1—5 h; iii, $RuCl_2(PPh_3)_3$ (0.02 equiv.), toluene, reflux 6 h.

Table 1. Indole (3a) from 2-aminophenethyl alcohol (2a).[a]

Run	Catalyst	Solvent	% Yield[b]
1	$RuCl_2(PPh_3)_3$	Toluene	100
2	$RuCl_2(PPh_3)_3$	*p*-Xylene	100
3	$RuCl_2(PPh_3)_3$	Diglyme	98
4	$RuCl_3 \cdot nH_2O$[c]	Toluene	2
5	$RuCl_3 \cdot nH_2O$[c]	Diglyme	5
6	$RuCl_3 \cdot nH_2O + PBu_3$[d]	Toluene	4
7	$RuCl_3 \cdot nH_2O + PBu_3$[d]	Diglyme	45

[a] Reactions were carried out under argon in the solvent under reflux for 6 h: (2a) (2.0 mmol), ruthenium compound [0.04 mmol; 2.0 mol% based on (2a)], solvent (5.0 ml). [b] Determined by g.l.c. [c] Ruthenium trichloride, mainly n = 3 (0.10 mmol). [d] $RuCl_3 \cdot nH_2O$ (0.04 mmol), PBu_3 (0.14 mmol); P/Ru = 3.5.

over a copper catalyst;[3] 0.6 equiv. of conc. HNO_3 at 220 °C[4]). We now report the first example of a homogeneously catalysed synthesis of indoles from (2).

2-Aminophenethyl alcohol (2a; R = H) is readily cyclised into indole (3a; R = H) in toluene under reflux. The reaction is effectively catalysed by $RuCl_2(PPh_3)_3$ to give (3a) in almost quantitative yields (Table 1, runs 1—3). The nature of the phosphorus ligand affects the catalytic activity considerably, triphenylphosphine (pK_a[5] 2.73; cone angle[6] 143°) being the best. Ruthenium(III) chloride itself shows only low catalytic activity (runs 4,5). Tributylphosphine (pK_a[5] 8.43; cone angle[6] 132°) is less effective (runs 6,7).

Representative 2-aminophenethyl alcohol derivatives (2b—d) are readily cyclised to the corresponding indoles (3b—d) in high yields (runs 9—11, Table 2) with spontaneous evolution of hydrogen. 4-Bromoindole (3d), a key intermediate in the synthesis of ergot alkaloids,[7] can be readily synthesised.

Kinetic features of the reaction were investigated. No induction period was observed. Plots of $[-\ln (1 - x/a_0)]$ *vs.*

Table 2. *N*-Heterocyclisation of 2-aminophenethyl alcohols (2a—d) into indoles (3a—d).[a]

Run	Indole		% Yield[b]	$k_{obs.}$[c] /$10^{-3}\,dm^3\,mol^{-1}\,s^{-1}$
8	(3a)	R = H	100	2.88
9	(3b)	R = 6-Me	(80)	3.27
10	(3c)	R = 4-Cl	(92)	6.50
11	(3d)	R = 4-Br	(73)	6.88

[a] In toluene under reflux for 6 h: (2) (7.0 mmol), $RuCl_2(PPh_3)_3$ (0.14 mmol), toluene (10 ml). [b] Determined by g.l.c. Figures in parentheses show isolated yields. [c] See equation (1).

time were linear for 75% conversions of (2), where x is the amount of (3) formed and a_0 is the amount of (2) charged. Furthermore, a straight line with a zero intercept was obtained on plotting the rate constants against the different initial catalyst concentrations ([Ru]$_0$ 6.10 × 10^{-3}—2.44 × 10^{-2} mol dm^{-3}). Thus the rate law for the present reaction may be expressed by equation (1). The $k_{obs.}$ values determined as above are listed in Table 2.

$$d[(3)]/dt = k_{obs.}[Ru]_0[(2)] \qquad (1)$$

The present *N*-heterocyclisation seems to proceed *via* indoline intermediates (4) produced by intramolecular *N*-alkylation of (2). Similar ruthenium-catalysed *N*-alkylations of amines with an alcohol functionality have been reported recently.[8,9] Indoline was dehydrogenated quantitatively into indole (3a) with spontaneous hydrogen evolution under the same conditions as for run 8, whereas 1,2,3,4-tetrahydroquinoline was not converted at all under the same conditions. The rate of dehydrogenation ($k_{obs.}$ = 2.03 × 10^{-2} dm^3 mol^{-1} s^{-1}) is about seven times faster than that of run 8 (Table 2). Thus, the rate law [equation (1)] can be derived by assuming a steady-state concentration of (4), which was confirmed by g.l.c. analyses.

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