CHEMISTRY LETTERS, pp. 603-604, 1980.

THE TRANSITION METAL-CATALYZED N-HETEROCYCLIZATION. THE RHODIUM-CATALYZED SYNTHESIS OF INDOLES

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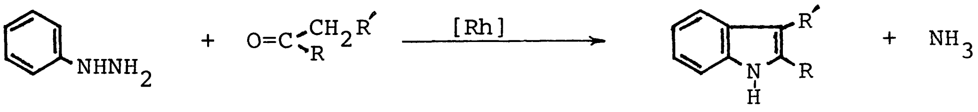
Substituted indoles can be prepared in high yields by the reaction between phenylhydrazine and carbonyl compounds at 180°C in the presence of a catalytic amount of a rhodium complex under non-acidic condition.

We recently reported that the rhodium-catalyzed reaction between aminoarenes and aliphatic aldehydes under non-acidic conditions afforded an efficient, synthetic method of quinolines.1) We herein wish to report a rhodium-catalyzed synthesis of indoles from phenylhydrazine and aldehydes or ketones. This is the first example of Fischer indole synthesis catalyzed by a transition metal complex under non-acidic conditions. Several methods for building up the indole nucleus under non-acidic conditions have been recently reported including the organometal-assisted intramolecular cyclization and photocyclization.2)



(1)

A typical procedure is illustrated as follows. A mixture of phenylhydrazine (40 mmol), an aldehyde or a ketone(40 mmol), μ,μ'-dichlorobis(cyclooctadiene)dirhodium(0.02 mmol), and ethanol(20 ml) was stirred under argon at 180°C for 4 h using a 100 ml autoclave. Products were separated by vacuum distillation or column chromatography and analyzed by means of IR, NMR spectra, and elemental analysis.

Phenylhydrazine reacted with a variety of aldehydes and ketones in the presence of a catalytic amount of $[RhCl(COD)]_2$ to give 3- or 2,3-substituted indoles in high yields. Representative results are listed in Table. Aliphatic aldehydes such as propanal, butanal, and pentanal gave 3-methyl-, 3-ethyl-, and 3-propylindole respectively. The NMR spectra of these products exhibited typical patterns assigned to the alkyl groups. The reaction proceeded smoothly at 180-200°C but at lower (160°C) or higher(220°C) temperatures, product yields decreased. Ketones also reacted with phenylhydrazine to give 2,3-substituted indoles in high yields. Butanone, 2- and 3-pentanone gave 2,3-dimethyl-, 2-methyl-3-ethyl-, and 2-ethyl-3-methylindole respectively. Cyclopentanone gave the corresponding substituted indole.

Rhodium complexes such as $RhCl_3 \cdot 3H_2O$, $RhCl_3Py_3$, $RhCl(PPh_3)_3$, and $[RhCl(NBD)]_2$

Table. The rhodium-catalyzed synthesis of indoles[a)]

Run	Carbonyl Compound	2,3-Substituted Indole 2-	3-	Isolated Yield (%)	^1H and ^{13}C NMR δ (ppm, Me_4Si)($CDCl_3$)
1	Propanal	H	CH_3	30 (49)[b)]	2.31 and 2.32(3H, CH_3), 6.88(s), 7.0-7.5(m)
2[c)]	Propanal	H	CH_3	(65)[b)]	
3	Butanal	H	CH_3CH_2	22	1.32(t,3,CH_3), 2.76(q,2,CH_2), 6.84(s), 7.0-7.7(m)
4	Pentanal	H	$CH_3CH_2CH_2$	30	0.91(t,3,CH_3), 1.63(m,2,CH_2), 2.63(t,2,CH_2), 6.59(s), 7.0-7.8(m)
5	Butanone	CH_3	CH_3	48	2.16(s,3,CH_3), 2.19(s,3,CH_3), 6.7-7.8(m)
6	2-Pentanone	CH_3	CH_3CH_2	39	1.13(t,3,CH_3), 1.95(s,3,CH_3), 2.60(q,2,CH_2), 7.0-7.6(m)
7	3-Pentanone	CH_3CH_2	CH_3	49	1.15(t,3,CH_3), 2.19(s,3,CH_3), 2.61(q,2,CH_2), 7.0-7.6(m)
8	Cyclopentanone	$-(CH_2)_3-$		59	24.3(t,CH_2), 25.6(t,CH_2), 28.5(t,CH_2), 111.2, 118.3, 119.3, 124.5, 130.2, 140.8 143.6

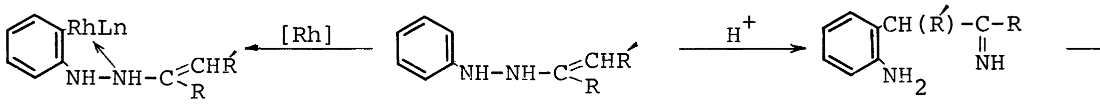
a) A mixture of phenylhydrazine(40 mmol), a carbonyl compound(40 mmol), $[RhCl(COD)]_2$ (0.02 mmol), and ethanol(20 ml) was treated at 180°C for 4 h.

b) Determined by GLC. c) At 200°C for 12 h.

catalyzed the reaction and the order of the catalytic activity of these complexes was the same as that of $[RhCl(COD)]_2$. Ethanol as the solvent was preferable to benzene and dioxane in this reaction.

An amine-imine type intermediate (3) has been reported for an acid-catalyzed Fischer indole reaction.[3)] The plausible mechanism of the present reaction seems to include an ortho-metalation step to form a rhodium containing intermediate (4). Ortho-metallated complexes are given by the reaction between N-containing compounds such as azobenzene and metal complexes.[4)]

The present procedure must be widely applicable for a variety of aliphatic aldehydes and ketones, leading to a synthetic route of substituted indoles.



(4) (2) (3) (1)

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3) See, for example: A.W. Douglas, J. Am. Chem. Soc., 101, 5676 (1979).

4) D.R. Fahey, J. C. S. Chem. Commun., 1970, 417; J. Organometal. Chem., 27, 283 (1971).

(Received March 24, 1980)