Palladium Complex-catalysed Reductive *N*-Heterocyclization of *N*-(2-Nitrobenzylidene)amines into 2*H*-Indazole Derivatives

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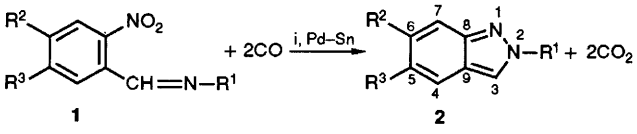
Dichlorobis(triphenylphosphine)palladium–tin(II) chloride system effectively catalyses the selective transformation of *N*-(2-nitrobenzylidene)amines into the corresponding 2*H*-indazole derivatives under carbon monoxide *via* a reductive *N*-heterocyclization reaction.

Although many interests in the chemistry of pyrazole and indazole derivatives have been stimulated because of their applications in industry and agriculture, and because of their biological and analytical importance,[1] little is known to the catalytic synthesis of these compounds.[2] Among the various possible methods for the construction of skeletons of these compounds, we are interested in transition metal complex-catalysed reductive *N*-heterocyclization[3] as well as reductive *N*-carbonylation[4] of nitro compounds. Herein, we report a novel palladium-catalysed synthesis of 2*H*-indazole derivatives from *N*-(2-nitrobenzylidene)amines *via* a reductive *N*-heterocyclization.

A typical procedure is as follows; a mixture of *N*-(2-nitrobenzylidene)amine (2.0 mmol), $PdCl_2(PPh_3)_2$ (0.10



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1a; R^1 = Ph, R^2, R^3 = H
b; R^1 = Pr^n, R^2, R^3 = OCH_2O
c; R^1 = Pr^n, R^2, R^3 = H
d; R^1 = Pr^i, R^2, R^3 = H
e; R^1 = Bu^t, R^2, R^3 = H
f; R^1 = Ph, R^2, R^3 = OCH_2O
g; R^1 = *m*-Cl-C_6H_4, R^2,R^3 = H

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Yield (%) **2a**; 48 (64)
b; 65
c; 62 (83)
d; 63
e; 75
f; 51
g; 74

Scheme 1 *Reaction conditions*: i, as for run 1; isolated yields (figures in parentheses are GLC yields)

Table 1 Catalytic activity of several transition metal complexes[a]

Run	Catalyst	Additive	Conv. (%)[b]	Yield (%)[b]
1	$PdCl_2(PPh_3)_2$	$SnCl_2$	100	64
2[c]	$PdCl_2(PPh_3)_2$	$SnCl_2$	100	43
3	$PdCl_2(PPh_3)_2$	$SnCl_4$	100	46
4	—	—	2	0
5	$PdCl_2(PPh_3)_2$	—	13	5
6	—	$SnCl_2$	45	2
7	$Pd(PPh_3)_4$	—	31	6
8	$PtCl_2(PPh_3)_2$	$SnCl_2$	100	51
9	$NiCl_2(PPh_3)_2$	$SnCl_2$	33	2
10	$RhCl(PPh_3)_3$	$SnCl_4$	51	3
11	$RuCl_2(PPh_3)_3$	$SnCl_2$	60	6

[a] *N*-(2-Nitrobenzylidene)aniline (2.0 mmol), catalyst (0.10 mmol), additive (1.0 mmol), THF (10 ml), CO 20 kg cm^{-2}, 100 °C, 16 h. [b] Determined by GLC. [c] $SnCl_2$ (0.20 mmol), 48 h.

mmol), $SnCl_2$ (1.0 mmol) and dry tetrahydrofuran (THF) (10 ml) was placed in a 50 ml stainless steel autoclave under 20 kg cm^{-2} of initial carbon monoxide and stirred at 100 °C for 16 h. The products were isolated by careful vacuum distillation and/or medium pressure column chromatography.

As shown in Scheme 1, the reductive *N*-heterocyclization of *N*-(2-nitrobenzylidene)amines **1a–g** smoothly proceeded in the presence of a palladium catalyst and $SnCl_2$ to give the corresponding 2*H*-indazole derivatives **2a–g**† in good to high yields.

The combination of $PdCl_2(PPh_3)_2$ with $SnCl_2$ was essential for the catalytic activity (runs 5 and 6 in Table 1). Other additives such as $ZnCl_2$, $AlCl_3$ and CuCl were ineffective. As for the catalysts, $PtCl_2(PPh_3)_2$ also showed moderate catalytic activity but the catalytic activities of other group VIII metal complexes were quite low (runs 8–11).

After the reaction, carbon dioxide was detected in gas phase (76% yield)‡ and it suggests that carbon monoxide would operate as a reductant of the nitro group.

The present reaction may be rationalized by assuming a nitrene intermediate. Firstly, deoxygenation of the nitro group in *N*-(2-nitrobenzylidene)amine by carbon monoxide would occur to give the nitrene intermediate.§ This electrophilic nitrene could attack the nitrogen atom of the imino substituent to give the corresponding indazole derivatives.[2b]

Mechanistic study and application of the present reaction are in progress.

Received, 9th May 1991; Com. 1/02192C

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† All compounds have been fully characterised by analysis and by spectroscopy. Analytical and spectral data of representative products (**2a** and **b**) are as follows (NMR measured in $CDCl_3$, chemical shifts are δ/ppm and relative to $SiMe_4$). Compound **2a**; white powder, m.p. 81.5–81.8 °C; ^{13}C NMR, δ 117.9 (d, indazole, C-7), 120.3 (d, indazole, C-5), 120.3 (d, indazole, C-4), 120.9 (d, phenyl, C-2), 122.4 (d, indazole, C-6), 122.8 (s, indazole, C-9), 126.8 (d, indazole, C-3), 127.8 (d, phenyl, C-4), 129.5 (d, phenyl, C-3), 140.5 (s, phenyl, C-1), 149.7 (s, indazole, C-8); mass spectrum (electron impact) *m/z* 194 (M^+, base peak).

Compound **2b**; yellow powder, m.p. 98.7–99.5 °C; ^1H NMR δ 0.92 (3H, t, Me), 1.97 (2H, m, CH_2CH_2Me), 4.24 (2H, t, CH_2CH_2Me), 5.92 (2H, s, OCH_2O), 6.84 [1H, s, indazole, (C-7) H], 6.98 [1H, s, indazole, (C-4) H], 7.66 [1H, s, indazole, (C-3) H]; ^{13}C NMR, δ 11.1 (q, CH_3), 23.8 (t, CH_2CH_2Me), 54.9 (t, CH_2Et), 93.9 (d, indazole, C-7), 94.7 (d, indazole, C-4), 100.5 (t, OCH_2O), 116.6 (s, indazole, C-9), 121.8 (d, indazole, C-3), 144.9 (s, indazole, C-5), 145.6 (s, indazole, C-6), 148.4 (s, indazole, C-8); mass spectrum (electron impact) *m/z* 204 (M^+), 175 ($M^+ - Et$, base peak).

‡ Theoretically, twofold of carbon dioxide based on *N*-(2-nitrobenzylidene) amine should be detected in gas phase and we now suppose that $SnCl_2$ would operate not only as a Lewis acid, but also as a reductant of nitro group.

§ Despite the interest in the reductive *N*-heterocyclization and *N*-carbonylation of nitroaromatics, remarkably few details have been established about the catalytic mechanism. Recently, Metz *et al.* reported the generation of a metallacyclic intermediate in the reductive *N*-carbonylation of nitrobenzene.[5] In the present reaction, however, carbon monoxide operates only as a reductant of the nitro group and was not incorporated into the product. So, the generation of isocyanate or such metallacyclic intermediates are thought to be unlikely. Although the mechanism *via* the nitroso intermediate is still considered viable, we now assume a nitrene intermediate, which would strongly coordinate to the metal, in the present reaction; such an intermediate has been postulated in the reductive *N*-carbonylation of nitroaromatics[4,6] and in the reduction of nitroso compounds.[7]