A New General Synthesis of *N*-Hydroxyindoles

Michel Belley,* Daniel Beaudoin, Gabriel St-Pierre

Department of Medicinal Chemistry, Merck Frosst Centre for Therapeutic Research, 16711 Trans-Canada Highway, Kirkland, QC, H9H 3L1, Canada
E-mail: belley@merck.com

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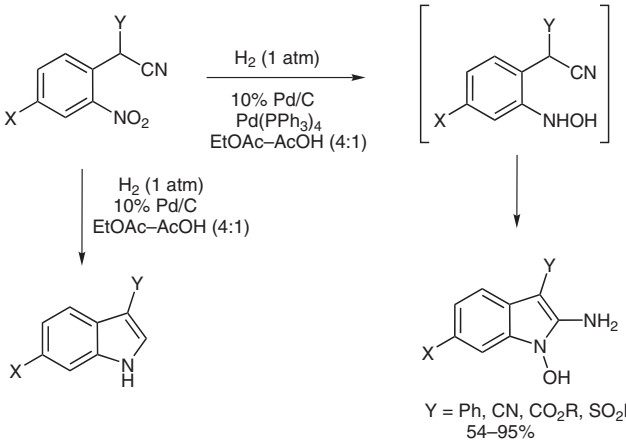
Abstract: Catalytic hydrogenation of 2-nitrobenzyl aldehydes, ketones and amides, using Pd/C and $(Ph_3P)_4Pd$, affords *N*-hydroxyindoles in good to excellent overall yields.

Key words: *N*-hydroxyindoles, *N*-methoxyindoles, reductive cyclization, tetrakis(triphenylphosphine)palladium, catalytic hydrogenation

The recent discovery of naturally occurring, bioactive *N*-hydroxyindoles such as nocathiacin I,[1] stephacidin B[2] and coproverdine,[3] and *N*-methoxyindoles (such as methoxybrassinin, paniculidine B, lespedamine and convolutindole A) has sparked the interest of the scientific community towards their synthesis.[4] In addition, the use of *N*-hydroxyindoles as intermediates and their hypothetical existence as metabolites in the enzymatic functionalization of indoles make the exploration of new routes for their preparation more attractive.

A variety of approaches have been reported to yield *N*-hydroxyindoles. Many of them rely on the reductive cyclization of *o*-nitrobenzyl aldehydes, ketones, esters, amides, nitriles or enamines using reagents such as Zn/AcOH,[5] $SnCl_2$,[6] H_2/Rh/C,[7] H_2/Pd,[8] $NaBH_4$/Pd or Pb/TEAF[9] (TEAF = triethylammonium formate). Also widely used are the base-promoted cyclization of *o*-nitroarylethane[10] and oxidations of indolines with $H_2O_2/NaWO_4$.[4] Finally, the coupling reactions between isonitriles and β-nitrostyrenes,[11] as well as between nitrosoarenes and alkynes,[12] are noteworthy. All these methods have their merits, but some are marred by issues such as lack of generality, poor chemoselectivity and yields, use of toxic heavy metals or high temperature at which *N*-hydroxyindoles are unstable.

We recently reported that catalytic hydrogenation of 2-nitrophenylacetonitriles bearing an electron-withdrawing group (EWG) or an aryl substituent α to the nitrile, using a mixture of Pd/C and $(Ph_3P)_4Pd$, afforded *N*-hydroxy-2-aminoindoles in good to excellent yields (Scheme 1).[13] In the absence of the EWG, we observed that the reductive cyclization to form the indole ring does not occur. Instead, we isolated mixtures of anilines and hydroxylamines originating from the reduction of the nitro group. The role of the co-catalyst $(Ph_3P)_4Pd$ has been found to be two-fold: It acts as a poisoning agent towards the Pd/C catalyst and it catalyzes the ring closure of the hydroxylamine intermediate onto the cyano group. In the absence of $(Ph_3P)_4Pd$, the reductive cyclization follows a different pathway leading exclusively to the formation of indoles that are unsubstituted at positions 1 and 2.



Scheme 1 Synthesis of *N*-hydroxy-2-aminoindoles having an electron-withdrawing substituent or an aryl group at position 3.

We wish to report herein new applications of this catalytic hydrogenation in which the cyclization occurs on amides, aldehydes and ketones, even in the presence of a nitrile group, to form a variety of *N*-hydroxyindoles in excellent yields.

While exploring the scope of the reductive cyclization and replacing the EWG α to the nitrile of 2-nitrophenylacetonitriles with amides,[14] we found that the reaction progressed via a different route (Table 1). Instead of cyclizing on the nitrile, the intermediate hydroxylamine reacted with the amide, forming an unstable 1,2-dihydroxy-3-cyanoindole **2** that could not be isolated cleanly. However, treatment of the crude reaction mixture with diazomethane afforded pure 1,2-dimethoxyindoles **3**. A similar reaction was also observed with the amidoester **4**, providing the 1,2-dimethoxyindole-3-carboxylate **6** in excellent yield (Scheme 2). This chemoselectivity towards the amide was a bit surprising in view of the fact that the reduction of the cyanoamide **7**, using zinc in AcOH, was reported to yield the 2-aminoindole **8**, with the amide intact at position 3 (Scheme 2).[5c] Moreover, catalytic hydrogenation of the cyanoamide **1b** and its analogues over Pd/C yields anilines or indole-3-carboxamides, depending on the temperature of the reaction.[15b]

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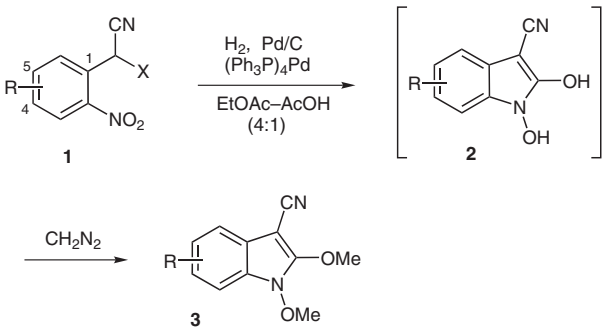
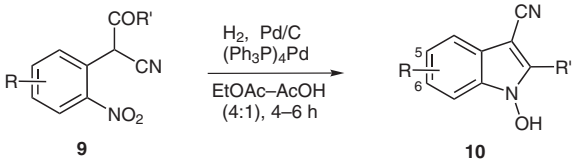
Table 1 Synthesis of 1,2-Dimethoxy-3-cyanoindoles



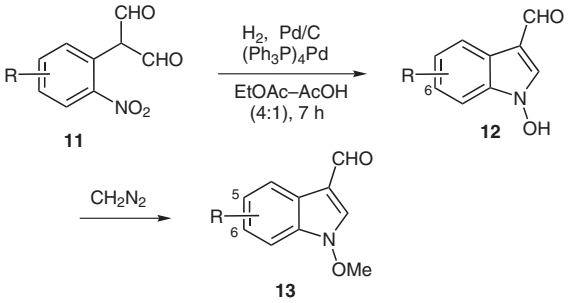
Cyanoamide	R	X	Reaction time (h)	**3**, Yield (%)
1a	4-CF_3	$CONH_2$	6.5	65
1b	4-CF_3	CONHPh	3	45
1c	5-Me	$CON(CH_2)_5$	23	61

Table 2 Synthesis of *N*-Hydroxy-3-cyanoindoles[17]



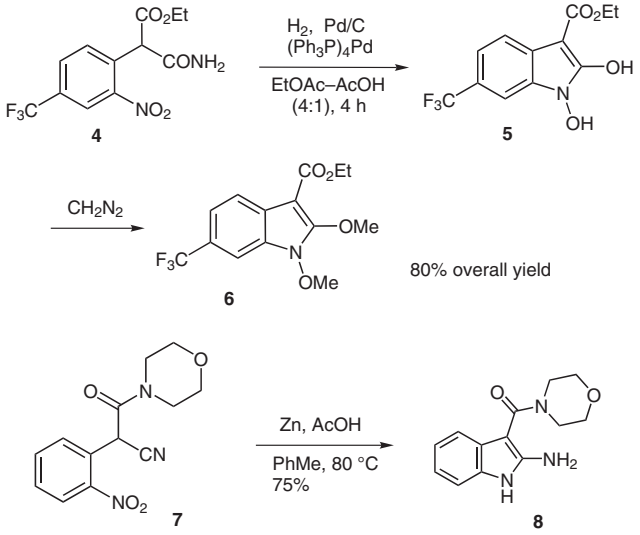
Cyanoketone	R	R′	**10**, Yield (%)
9a	5-Me	Me	92
9b	6-CF_3	*t*-Bu	96
9c	6-F	Ph	98

Table 3 Synthesis of *N*-Hydroxyindole-3-carboxaldehydes



Dialdehyde	R	**12**, Yield (%)	**13**, Yield (%)
11a	H	80	75
11b	5-Cl	59	81
11c	6-MeO	43	75

Table 2 summarizes the results obtained with ketones as the EWG. Reductive cyclization of cyanoketones **9** provided *N*-hydroxy-3-cyanoindoles **10**, substituted at C-2 by an alkyl or an aryl group, in excellent yields. The *o*-nitrophenyl malonaldehydes **11** were found to react in the same manner, providing *N*-hydroxyindole-3-carbaldehydes **12** (Table 3). Treatment of **12a** with diazomethane afforded the natural product *N*-methoxyindole-3-carbaldehyde (**13a**) in two steps with an unoptimized overall yield of 60%. This compound has been isolated from the Cruciferae family of plants[16] and is an intermediate in the synthesis of many other natural products, including methoxybrassinin, paniculidine B and lespedamine.[4]

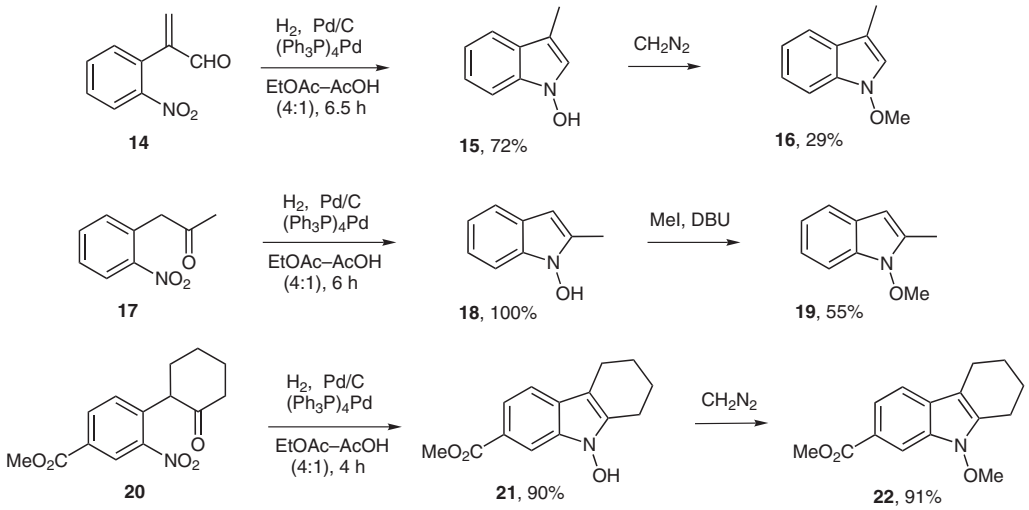


Scheme 2

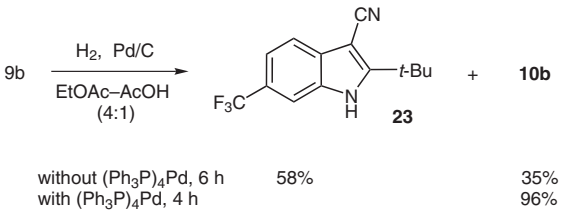
We have reported that in order for the reductive cyclization to occur on the nitrile, either an EWG or an aromatic substituent α to the nitrile function was necessary. With ketones, that substituent is no longer required, as exemplified in Scheme 3 with the synthesis of *N*-hydroxyindoles **18** and **21**. Noteworthy was the hydrogenation of the unsaturated aldehyde **14** where the double bond was also reduced to afford *N*-hydroxy-3-methylindole (**15**).

The role of the co-catalyst $(Ph_3P)_4Pd$ in all the transformations shown here might be slightly different from what we have published previously with *o*-nitrophenylacetonitriles. For example, the reductive cyclization of the cyanoketone **9b** over Pd/C and the co-catalyst $(Ph_3P)_4Pd$ yielded exclusively **10b**[17] (Table 2 and Scheme 4). However, in the absence $(Ph_3P)_4Pd$, a mixture of the *tert*-butyl indole **23** and the *N*-hydroxyindole **10b** was obtained. Using the same conditions with nitriles, the unsubstituted indoles were produced exclusively. The intermediate hydroxylamines probably react readily with aldehydes and ketones and $(Ph_3P)_4Pd$ is not likely catalyzing this cyclization to afford the *N*-hydroxyindoles. The major role of the co-catalyst might be to reduce the speed of the reduction of the nitro group to the amine, so that the hydroxylamine intermediate would survive longer in the reaction medium and have more time to cyclize onto the carbonyl functionality.

In summary, we have given here examples of a new reductive cyclization of *o*-nitrobenzyl amides, aldehydes and ketones leading to the generation of a large variety of *N*-hydroxyindoles in good to excellent yields. This transformation, which requires only a simple hydrogenation over



Scheme 3 Reductive cyclization on *o*-nitrobenzyl ketones



Scheme 4

Pd/C in the presence of $(Ph_3P)_4Pd$ as a co-catalyst, was also applied successfully to the synthesis of the naturally occurring *N*-methoxyindole-3-carbaldehyde (**13a**).

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(14) Most of the substrates used for the reductive cyclization were prepared by aromatic electrophilic substitution, either with NaH in DMF[15] (**1a–c**, **4** and **9c**) or NaOH/TBAHS/toluene[18] (**9a**,**b**). Compounds **11a–c**, **14** and **17** were commercially available and **20** was prepared via a Pd-catalyzed arylation of a ketone enolate.[9]

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(17) **Typical Experimental Procedures**: **2-*tert*-Butyl-1-hydroxy-6-(trifluoromethyl)-1*H*-indole-3-carbonitrile (10b)**: To a solution of 4,4-dimethyl-2-[2-nitro-4-(trifluoromethyl)phenyl]-3-oxopentanenitrile (**9b**; 236 mg, 0.75 mmol) in a mixture of EtOAc and AcOH (4:1, 12 mL) were added 10% Pd/C (40 mg, 0.05 equiv) and $(Ph_3P)_4Pd$ (13 mg, 0.015 equiv). This mixture was degassed and stirred under an atmosphere of hydrogen for 4 h. The solids were removed by a filtration through Celite and the solvents were evaporated. Flash chromatography of the residue on silica gel using a gradient of EtOAc–hexane (0–25%) as eluent afforded **10b** (204 mg, 96% yield) as a light beige powder; mp 144 °C (dec.). ^{1}H NMR (400 MHz, acetone-d_6): δ = 11.07 (s, 1 H), 7.84 (s, 1 H), 7.81 (d, J = 8.3 Hz, 1 H), 7.58 (dd, J = 1.3, 8.3 Hz, 1 H), 1.69 (s, 9 H). ^{13}C NMR (100 MHz, acetone-d_6): δ = 153.78, 133.02, 126.60, 125.14 (q, J_{C-F} = 32 Hz), 124.91 (q, J_{C-F} = 269 Hz), 119.19,

118.34 (q, J_{C-F} = 4 Hz), 115.47, 106.68 (q, J_{C-F} = 4 Hz), 78.60, 34.48, 28.51. IR (KBr): 3127, 2977, 2229 (CN), 1365, 1324, 1272, 1119 cm^{-1}. MS (ESI, +ve): *m*/*z* = 283.0 [M + 1]. Anal. Calcd for $C_{14}H_{13}F_3N_2O$: C, 59.57; H, 4.64; N, 9.92. Found: C, 59.47; H, 4.68; N, 9.55.

Ethyl 1,2-Dimethoxy-6-(trifluoromethyl)-1*H*-indole-3-carboxylate (6): The reductive cyclization of ethyl 3-amino-2-[2-nitro-4-(trifluoromethyl)phenyl]-3-oxopropanoate (**4**; 270 mg, 0.75 mmol) was performed as described above. The crude material obtained after filtration was redissolved into THF and treated with an ethereal solution of CH_2N_2 at r.t. for 45 min. The excess CH_2N_2 was quenched with AcOH, the solvents were evaporated and the residue was purified by flash chromatography on silica gel using a gradient of EtOAc–hexane (0–10%) as eluent to give dimethoxyindole **6** (191 mg, 80%) as a light beige powder; mp 76 °C. ^{1}H NMR (400 MHz, acetone-d_6): δ = 8.25 (d, *J* = 8.4 Hz, 1 H), 7.78 (s, 1 H), 7.52 (dd, *J* = 1.3, 8.4 Hz, 1 H), 4.40 (q, *J* = 7.1 Hz, 2 H), 4.38 (s, 3 H), 4.24 (s, 3 H), 1.43 (t, *J* = 7.1 Hz, 3 H). ^{13}C NMR (100 MHz, acetone-d_6): δ = 162.69, 155.17, 126.75, 125.10 (q, J_{C-F} = 269 Hz), 123.91 (q, J_{C-F} = 32 Hz), 123.75, 121.65, 118.50 (q, J_{C-F} = 4 Hz), 105.28 (q, J_{C-F} = 4 Hz), 88.54, 66.29, 63.39, 59.53, 13.90. IR (KBr): 2987, 2949, 1703, 1555, 1459 cm^{-1}. MS (ESI, +ve): *m*/*z* = 318.0 [M + 1], 289.1, 229.0. Anal. Calcd for $C_{14}H_{14}F_3NO_4$: C, 53.00; H, 4.45; N, 4.41. Found: C, 53.20; H, 4.13; N, 4.30.

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