ELSEVIER

Synthesis and reactivity of *N*-hydroxy-2-aminoindoles

Michel Belley,* Effiette Sauer, Daniel Beaudoin, Petar Duspara, Laird A. Trimble
and Pascal Dubé

*Merck Frosst Centre for Therapeutic Research, PO Box 1005, Pointe Claire-Dorval, Québec, Canada H9R 4P8*

Abstract—Catalytic hydrogenation of (2-nitrophenyl)acetonitriles bearing an electron-withdrawing substituent α to the nitrile, using Pd/C and $(Ph_3P)_4Pd$, affords *N*-hydroxy-2-aminoindoles in good to excellent yields. $(Ph_3P)_4Pd$ decreases the reduction rate of the intermediate hydroxylamine and acts as a catalyst during the cyclization onto the nitrile.
© 2005 Elsevier Ltd. All rights reserved.

The synthesis of *N*-hydroxyindoles has received considerable attention in recent years and their biological roles are still under investigation.[1,2] Some of them have been isolated from natural sources and others have been postulated as intermediates in the enzymatic functionalization of indoles. However, there are very few reports in the literature on the formation of *N*-hydroxy-2-amino-indoles[3] and their biological activity is unknown, although they were used as intermediates in the synthesis of potent anticonvulsant and antiarrhythmic agents.[3a,4]

2-Cyano-2-(2-nitrophenyl)acetates **1** have been used extensively as key intermediates in the synthesis of indole derivatives (Scheme 1). Catalytic hydrogenation of **1** over Pd/C in EtOAc affords indole-3-carboxylates **2**[5] or, when R is a benzyl group, 2,3-unsubstituted indoles **3**.[6] Hydrogenation of **1** (R = Et) over Pd/C in toluene–EtOH yields the corresponding aniline, which can then react with benzaldehyde to give the indoline **4**.[7] Reduction of **1** with zinc powder in acetic acid at 80–100 °C generates 2-aminoindole-3-carboxylates **5**.[8] However, when this reduction is performed at lower temperature (or when $SnCl_2$ is used as the reducing agent),[3c] *N*-hydroxy-2-aminoindoles **6** are obtained as major products in 20–66% yields.[3a,b]

During the course of our research, we found that catalytic hydrogenation of **1** over Pd/C in the presence of
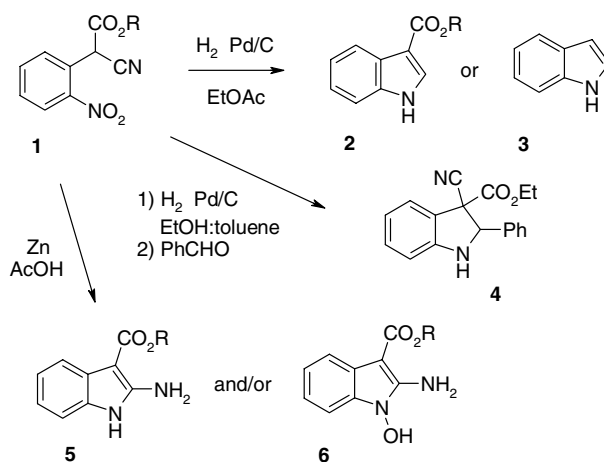
Scheme 1.

$(Ph_3P)_4Pd$ no longer affords indoles **2**. Instead, *N*-hydroxy-2-aminoindoles **6** are obtained almost exclusively. We wish to report herein this new and unprecedented method for the synthesis of **6**, along with its mechanism. Results from experiments on the reactivity of *N*-hydroxy-2-aminoindoles **6** will also be discussed.

In order to explore the scope of this novel reductive cyclization, several analogs of **1** were prepared from the reaction of 2-nitrofluorobenzenes or 2-nitrochlorobenzenes with the anions of ethyl cyanoacetate, cyanomethyl sulfones or malononitrile, using either NaH in DMF (**1a–g**)[3a,9] or NaOH and Bu_4NHSO_4 in toluene (**1h–j**).[10,11] Catalytic hydrogenation of these (2-nitrophenyl)acetonitriles over Pd/C in the presence of

Table 1. Reductive cyclization of (2-nitrophenyl)acetonitriles to *N*-hydroxy-2-aminoindoles

Substrate no	X	Y	6, Yield (%)	7, Yield (%)
1a	CF$_3$	CO$_2$Et	78	98
1b	H	CO$_2$Et	86	
1c	MeO	CO$_2$Et	72	91^d
1d	Cl	CO$_2$Et	75	94, 96^d
1e	MeSO$_2$	CO$_2$Et	54	69^a
1f	AcNH	CO$_2$Et	75^c	
1g	CF$_3$	SO$_2$Me	72	55^d
1h	CF$_3$	SO$_2$Ph	90	
1i	F	SO$_2$Ph	94^c	
1j	CF$_3$	CN	64^{b,c}	

^{a} Overall yield from **1**, without purification of **6**.
^{b} The tetrabutylammonium salt of the (2-nitrophenyl)malononitrile was used as the starting material.
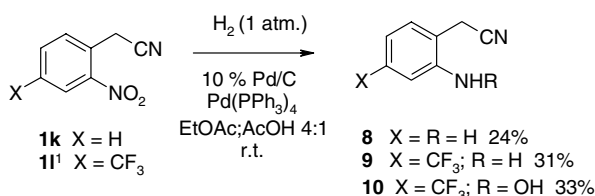^{c} Reaction time 5 h.
^{d} Methylation with MeI and DBU (3 equiv each) in THF at rt for 1.5 h.

(Ph$_3$P)$_4$Pd gave *N*-hydroxy-2-aminoindoles **6a–j** in good to excellent yields (Table 1).[12,13] *O*-Methylation of **6**, with diazomethane (rt, 15 min) or MeI and DBU, afforded *N*-methoxy-2-aminoindoles **7** as more stable derivatives (vide infra).

The reductive cyclization proceeded well when the substituent α to the nitrile Y (Table 1) is an electron-withdrawing group. However, when Y is a hydrogen or a methyl group, the corresponding *N*-hydroxy-2-amino-indoles were not detected. The cyclization leading to the formation of indole did not occur and the major products isolated were the anilines and/or the hydroxyl-amines resulting from the reduction of the nitro group (Scheme 2).

The presence of Pd(PPh$_3$)$_4$ is crucial for the reaction and it serves two purposes. First, it acts as a poisoning agent towards the Pd/C catalyst by modifying the chemoselectivity of the reduction of the nitro functionality. When 3-nitrobenzotrifluoride **11** is hydrogenated over Pd/C, the nitro group is completely reduced to the aniline **12** (Fig. 1). However, treatment of **11** with (Ph$_3$P)$_4$Pd under the same reaction conditions afforded the hydroxyl-amine **13** in 38% yield, along with some aniline **12**.

Replacement of (Ph$_3$P)$_4$Pd with PdCl$_2$(dppf) did not affect the course of the reaction since **6b** could still be obtained in 70% yield. On the other hand, only traces of **6b** were detected when (Ph$_3$P)$_4$Pd was substituted with Pd$_2$(dba)$_3$ for the reductive cyclization. This result suggests that the palladium ligand is possibly poisoning the Pd/C catalyst. Although addition of triphenylphosphine to Pd/C did not interfere with the reduction of **1b** to the indole **2** (R = Et), heating Pd/C in a solution of Ph$_3$P in EtOAc for 15 min at 75 °C prior to the hydrogenation produced the *N*-hydroxy-2-aminoindole **6b** in 53% yield. The poisoning effect of (Ph$_3$P)$_4$Pd might be due to a Pd(0) catalyzed Ph$_3$P transfer to the Pd/C catalyst.

In addition, Pd(PPh$_3$)$_4$ catalyzes the ring closure of the hydroxylamine intermediate onto the cyano group. This second role was confirmed when the unstable reaction intermediate **14** readily cyclized in the presence of Pd(PPh$_3$)$_4$ to generate **6i** (82% yield, Scheme 3). The hydroxylamine **14**, which decomposed in EtOAc and AcOH solutions in the absence of catalyst, was synthesized by reduction of the (nitrophenyl)acetonitrile **1i** with sodium hypophosphite.[14]

N-Hydroxy-2-aminoindoles **6** are usually stable when stored at 5 °C. However, derivatization or reduction of *N*-hydroxy functionality has been found to increase the stability of these compounds. For example, the *N*-hydroxy-2-aminoindole **6b** can be reduced to the 2-aminoindole **5b** by catalytic hydrogenation in ethanol under pressure[15] (Scheme 4). *N*-Hydroxy substituent can also be alkylated with an alkyl or a benzyl bromide (Scheme 4),[4] or methylated with diazomethane at room temperature (Table 1). Finally, it can be acylated with acetic anhydride in pyridine.[3a] However, the resulting N-acylated compound **15c** is not very stable and can be hydrolyzed easily to afford **6a** (in the refrigerator over a period of weeks or by refluxing in methanol for 10 min).

The 2-amino functionality is fairly unreactive under basic conditions. *N*-Alkylation does not occur when the *N*-hydroxy substituent is alkylated, even in the presence of a large excess of alkylating agent at high temperatures. Furthermore, acylation of **7d** proceeded only
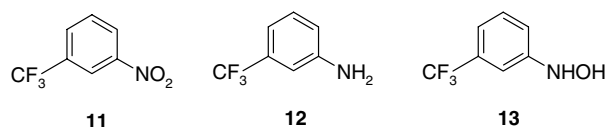
Figure 1.
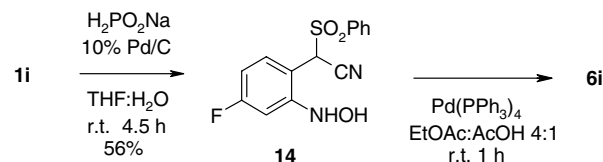
Scheme 2.
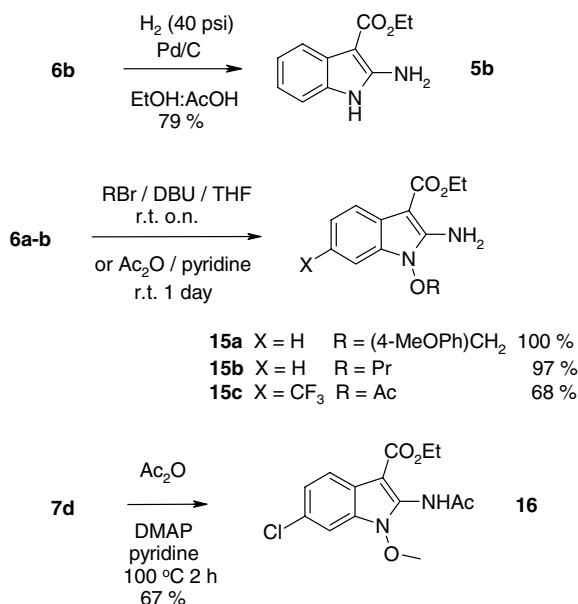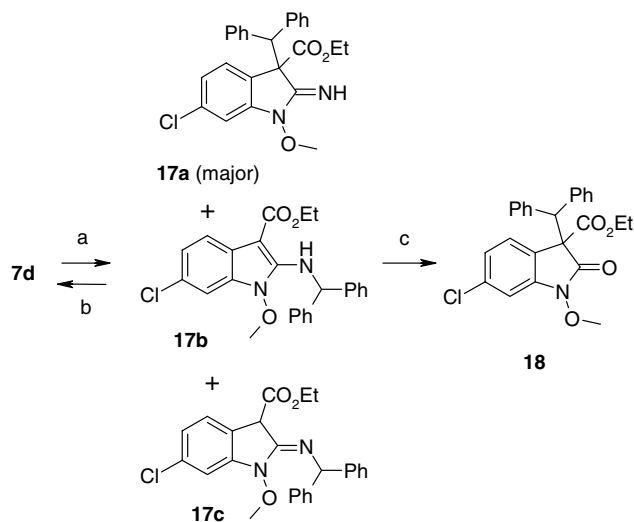
Scheme 3.

Scheme 4.

Scheme 5. Reagents and conditions: (a) Ph₂CHOH, cat. H₂SO₄, AcOH, rt, 16 h, 80%; (b) aq HCl, THF; (c) 2 N HCl, pyridine, rt, 4 days, 83%.

under forceful conditions (Scheme 4). These results suggest that this amine reacts more like a vinylogous carbamate than like an arylamine.

Acid-catalyzed alkylation of amides, carbamates and anilines with diarylcarbinols has been reported to occur readily in acetic acid at room temperature.[16] The resulting diarylmethyl substituents were used as protecting groups in synthesis.[16b] Reaction of **7d** with diphenylcarbinol under these acid-catalyzed conditions yielded a mixture of three inseparable compounds **17a–c** (single peak on HPLC, Scheme 5), which are in equilibrium with each other in solution.[17] These products could be hydrolyzed back to the starting material with HCl in THF or converted to the oxindole **18** with aqueous

HCl in pyridine.[18] Moreover, reaction of **17a–c** with acetyl chloride in THF at rt for 3 days afforded the N-acylated derivative **16** in 53% unoptimized yield.

In summary, we have demonstrated that *N*-hydroxy-2-aminoindoles bearing an electron-withdrawing substituent in position 3 can be prepared in good yields via hydrogenation with a modified Pd/C catalyst. The addition of Pd(Ph₃P)₄ to the hydrogenation mixture was found to alter the chemoselectivity of the reaction, an effect that, to our knowledge, has not been reported previously.

New applications of this reaction towards the synthesis of hydroxylamines and other *N*-hydroxyindoles are currently under investigation.

Supplementary data

Physical data for all the new compounds described in this article can be found in the online version. Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2005.10.165.

References and notes

1. Wong, A.; Kuethe, J. T.; Davies, I. W. *J. Org. Chem.* **2003**, *68*, 9865–9866, and references cited therein.
2. For reviews on *N*-hydroxyindoles, see: (b) Somei, M. *Adv. Heterocycl. Chem.* **2002**, *82*, 101–155; (c) Somei, M. *Heterocycles* **1999**, *50*, 1157–1211.
3. (a) Munshi, K. L.; Kohl, H.; de Souza, N. J. *J. Heterocycl. Chem.* **1977**, *14*, 1145–1146; (b) Showalter, H. D. H.; Bridges, A. J.; Zhou, H.; Sercel, A. D.; McMichael, A.; Fry, D. W. *J. Med. Chem.* **1999**, *42*, 5464–5474; (c) Stephensen, H.; Zaragoza, F. *Tetrahedron Lett.* **1999**, *40*, 5799–5802.
4. Munshi, K. L.; Bhattacharyya, B. K.; Dohadwalla, A. H. N.; de Souza, N. J.; Kohl, H. Indian Pat. Appl. 75-BO108, 1975; *Chem. Abstr.* **1980**, *92*, 163840.
5. (a) Belley, M.; Scheigetz, J.; Dubé, P.; Dolman, S. *Synlett* **2001**, 222–225; (b) Snyder, H. R.; Merica, E. P.; Force, C. G.; White, E. G. *J. Am. Chem. Soc.* **1958**, *80*, 4622–4625, and references cited therein; for similar reductions, see: (c) Bourdais, J.; Germain, C. *Tetrahedron Lett.* **1970**, *11*, 195–198, and references cited therein.
6. Walkington, A.; Gray, M.; Hossner, F.; Kitteringham, J.; Voyle, M. *Synth. Commun.* **2003**, *33*, 2229–2233.
7. Dijkink, J.; Zonjee, J. N.; de Jong, B. S.; Speckamp, W. N. *Heterocycles* **1983**, *20*, 1255–1258.
8. (a) Forbes, I. T.; Morgan, H. K. A.; Thompson, M. *Synth. Commun.* **1996**, *26*, 745–754; (b) Glushkov, R. G.; Volokova, V. A.; Yu, O. *Khim. Farm. Zh.* **1967**, *1*, 25–32; *Chem. Abstr.* **1968**, *68*, 105143f; (c) Reduction with SnCl₂ and HCl in ether has also been reported to yield 2-aminoindoles.[5b]

9. (a) Grob, C. A.; Weissbach, O. *Helv. Chim. Acta* **1961**, *44*, 1748–1753; (b) Scobie, M.; Tennant, G. *J. Chem. Soc., Chem. Commun.* **1993**, 1756–1757.

10. Makosza, M.; Tomashewskij, A. A. *J. Org. Chem.* **1995**, *60*, 5425–5429.

11. Tetrabutylammonium dicyano[2-nitro-4-(trifluoromethyl)phenyl]methanide **1j** was prepared by treating 1-chloro-2-nitro-4-(trifluoromethyl)benzene (8.9 mmol) with malononitrile (1 equiv), Bu_4NHSO_4 (1 equiv) and 10 N NaOH (6.8 equiv) in toluene (30 mL) at 70 °C for 4.3 h.[10] When the reaction was complete, water was added and the tetrabutylammonium salt **1j** was extracted with EtOAc and purified by flash chromatography on silica (10% $MeOH/CH_2Cl_2$) to afford a bright red powder (82% yield).

12. General procedure for the formation of *N*-hydroxy-2-aminoindoles. To a solution of (2-nitrophenyl)acetonitrile **1a**–**j** (0.70 mmol) in EtOAc–AcOH 4:1 (5 mL) was added 10% Pd/C (22 mg, 2.0 mol %) and $Pd(PPh_3)_4$ (12 mg, 1.5 mol %) and this mixture was stirred under an atmosphere of hydrogen for 3 h. The catalyst was removed by filtration through Celite and the solvents were evaporated in vacuo. The crude product was purified by flash chromatography.

13. Physical data for compounds **6b**–**d**,**f** are in good agreement with the published data.[3a] The novel *N*-hydroxy-2-amino-indoles and their derivatives were characterized by ^{1}H NMR, ^{13}C NMR, IR, MS, elemental analysis and/or HRMS.

14. The unstable intermediate [4-fluoro-2-(hydroxyamino)-phenyl](phenylsulfonyl)acetonitrile **14** was prepared using the method of Entwistle, I. D.; Gilkerson, T.; Johnstone, R. A. W.; Telford, R. P. *Tetrahedron* **1978**, *34*, 213–215, The crude product was purified by flash chromatography on silica, with each fraction collected being cooled down to −78 °C and kept under N_2 as much as possible. Concentration of the fractions containing **14** was done in vacuo without heating above 20 °C.

15. For similar reduction of *N*-hydroxyindoles, see: Penoni, A.; Volkmann, J.; Nicholas, K. M. *Org. Lett.* **2002**, *4*, 699–701.

16. (a) Henneuse, C.; Boxus, T.; Tesolin, L.; Pantano, G.; Marchand-Brynaert, J. *Synthesis* **1996**, 495–501; (b) Laurent, M.; Marchand-Brynaert, J. *Synthesis* **2000**, 667–672, and references cited therein.

17. ^{1}H NMR spectra in methanol-d₄, acetone-d_6 and DMSO-d_6 solutions display many broad peaks, which coalesce to a smaller number of broad peaks at higher temperature (100 °C in DMSO-d_6). The structure of the major isomer ethyl 6-chloro-3-(diphenylmethyl)-2-imino-1-methoxyindoline-3-carboxylate **17a** was fully established by performing ROESY NMR studies (600 MHz, in DMSO-d_6 with some TFA to give sharp peaks).

18. The structure of ethyl 6-chloro-3-(diphenylmethyl)-1-methoxy-2-oxoindoline-3-carboxylate **18** was fully established from 600 MHz NMR studies (NOESY, gCOSY, gHSQC and gHMBC).