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Synthesis of 2-Aminoindole Derivatives with Hantzsch Ester Catalyzed by Pd/C

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Catalytic hydrogenation of 2-cyano-2-(2-nitrophenyl)acetates bearing an electron withdrawing substituent to the nitrile, using Hantzsch ester catalyzed by Pd/C, affords 2-aminoindoles in good to excellent yields.

Keywords 2-aminoindole, reductive cyclization, Hantzsch ester, palladium on carbon

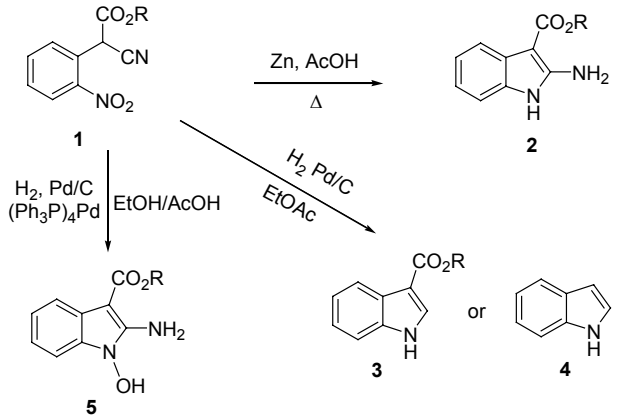
Introduction

2-Aminoindoles can be precursors for many pharmacologically active compounds such as 2-diazoindoles and 2-triazenoindoles, the latter related to a triazenoimidazole derivative, dacarbazine, which is currently utilized in therapy against malignant melanoma and Hodgkin's disease.[1] 2-Aminoindoles are also useful building blocks for the preparation of new ring systems, such as the indolo[2,1-*d*]-[1,2,3,5]tetrazine related to temozolomide, the antitumour drug active against malignant melanoma, mycosis fungoide and brain tumours.[2]

To date, many synthetic methods have been developed for the synthesis of 2-aminoindoles. 2-Cyano-2-(2-nitrophenyl)acetates **1** have been extensively used as key intermediates in the synthesis of indole derivatives by reductive cyclization (Scheme 1).

Reductive cyclization of **1** with zinc powder in acetic acid at high temperature currently is a common approach for the synthesis of 2-aminoindoles **2**.[3] However, both zinc powder and acidic condition unfit environmental points of view. Therefore, it is much desirable to develop a novel method for this kind of transformation. Hydrogen has been widely used for the reductive cyclization of **1**. For instance, catalytic hydrogenation of **1** over Pd/C affords indole-3-carboxylates **3**[3c,4] or 2,3-unsubstituted indoles **4**,[5] and in the presence of $(Ph_3P)_4Pd$ gives *N*-hydroxy-2-aminoindoeles **5**.[6] To our knowledge, the production of 2-aminoindole derivatives can not be easily achieved by hydrogen molecules in the previous researches

Scheme 1



Hantzsch 1,4-dihydropyridine (HEH) has been widely used as a model compound of coenzyme NAD(P)H,[7] which plays a pivotal role in biochemical redox processes. Recent studies in our laboratory have shown that the reducibility of HEH is dramatically enhanced in the presence of Pd/C.[8] Moreover, high chemoselectivities have been achieved by regulating reaction conditions, such as the amount of HEH, reaction temperatures and solvents. We have examined the selective reduction of a nitro group with HEH and Pd/C in the presence of epoxy, ester or amide substituents could successfully accomplished the synthesis of 2*H*-1,4-benzoxazine,[8c] benzoxazole,[8e] benzimidazole[8e] and quinoline[8f] derivatives. Herein, we wish to report a novel method that 2-aminoindoles can be efficiently synthesized via Pd/C-catalyzed intra-molecular reductive cyclization in the presence of HEH.

Experimental

^{1}H NMR and ^{13}C NMR spectra were recorded with a

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Varian instrument (300 and 75 MHz, respectively) and internally referenced to the tetramethylsilane signal or residual protio solvent signals. Mass spectra were recorded by EI methods. HRMS data were determined with a Bruker Daltonics APEXII 47e FTICR spectrometer. All reactions under standard conditions were monitored by thin-layer chromatography (TLC) on gel F254 plates. Silica gel (200—300 mesh) was used for column chromatography. The employed solvents were dried by the standard procedures. Commercially obtained reagents were used without further purification.

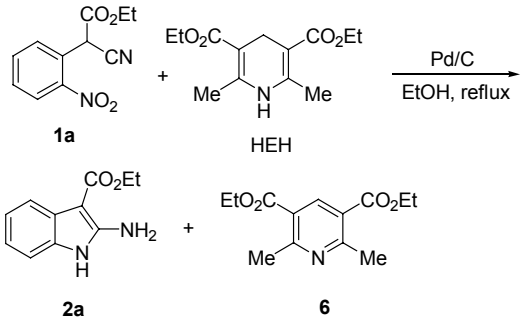
Typical procedure for synthesis of product

To the CH_3CH_2OH solution (25 mL) of substrate (1.0 mmol) were added HEH (3.5 mmol) and 10% Pd/C (20 wt% of substrates), the mixture was refluxed under argon atmosphere by stirring for 10 h. After completion, the reaction was monitored by TLC, the solution was filtered and the filtrate was concentrated under reduced pressure. The corresponding compounds were isolated by a column chromatography (silica gel).

Results and Discussion

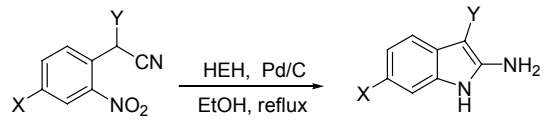
We found that refluxing ethyl 2-nitrophenylcyanoacetate (**1a**) with HEH in the presence of 10 % Pd/C in ethanol generated 2-amino-3-carbethoxyindole (**2a**), besides **2**, another product was also obtained, which was characterized to be diethyl 2,6-dimethyl-3,5-pyridinedicarboxylate **6** (Scheme 2). The amount of Pd/C mainly influences the reaction time. For instance, the reaction of **2a** and 3.5 equiv. of HEH completed within 7 h in the presence of 25 wt% of substrates of Pd/C, while 15 h were needed when the amount of Pd/C decreased to 10 wt%. No reaction took place in the absence of Pd/C under the same conditions. 20 wt% of substrates of Pd/C was finally selected in this work, since the reaction could complete well in 10 h.

Scheme 2



We can conclude from Table 1 that the method was successfully extended to synthesize some 2-aminoindoles. Substrates with electron-donating groups in the phenyl nucleus (**1d**) and bulky esters α to the nitrile (**1c**) gave desired products in lower yields. The best yield was got when the substituent α to the nitrile Y was the methoxycarbonyl group (**1f**). However, when substituent Y was the cyano or trifluoromethyl group, the products obtained were not only 2-aminoindoles **2** but also *N*-hydroxy-2-aminoindoeles **5** (Table 2). It seems that the yields of **5** increased with the enhancement of electron-withdrawing abilities of substituent X and Y. Reductive cyclization of **1k** only produced the corresponding *N*-hydroxy-2-aminoindoeles **5** in 80.2% yield.

Table 1 Synthesis of 2-aminoindole derivatives with 2-cyano-2-(2-nitrophenyl)acetates **1** by HEH[a]

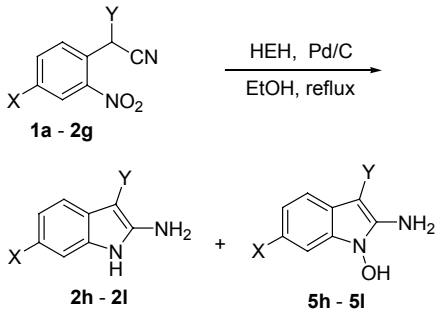


1a - **1g** **2a** - **2g**

Substrate	X	Y	Product	Yield[b]/%
1a	H	CO_2Et	**2a**	70.9
1b	H	CO_2Me	**2b**	69.5
1c	H	CO_2Bu^t	**2c**[c]	53.4
1d	Me	CO_2Et	**2d**	53.0
1e	CO_2Me	CO_2Et	**2e**[c]	75.2
1f	CO_2Me	CO_2Me	**2f**[c]	80.4
1g	CO_2Me	CO_2Bu^t	**2g**[c]	80.0

[a] Reaction conditions: a mixture of 2-cyano-2-(2-nitrophenyl) acetates (**1**, 1 mmol) and HEH (3.5 mmol) in 25 mL of ethanol containing 10% Pd/C (20 wt% of substrates) was refluxed under stirring and argon atmosphere in 10 h. [b] Isolated yields. All products were characterized by EI-MS, ^{1}H NMR and ^{13}C NMR. [c] Products are unknown compounds. All products were characterized by EI-MS, ^{1}H NMR, ^{13}C NMR and HRMS.

Table 2 Reductive cyclization of 2-cyano-2-(2-nitrophenyl)-acetates **1** by HEH[a]



1a - **2g** **2h** - **2l** **5h** - **5l**

Substrate	X	Y	Product	Yield[b]/%
1h	CN	CO_2Et	**2h**, **5h**[c]	30.3 (**2h**), 48.4 (**5h**)
1i	CF_3	CO_2Et	**2i**, **5i**	16.9 (**2i**), 60.0 (**5i**)
1j	CF_3	CO_2Me	**2j**, **5j**[c]	17.2 (**2j**), 68.5 (**5j**)
1k	CF_3	SO_2Ph	**5k**	80.2

[a] Reaction conditions: a mixture of 2-cyano-2-(2-nitrophenyl)-acetates (**1**, 1 mmol) and HEH (3.5 mmol) in 25 mL of ethanol containing 10 % Pd/C (20 wt% of substrates) was refluxed under stirring and argon atmosphere in 10 h. [b] Isolated yields. All products are known compounds and were characterized by EI-MS, ^{1}H NMR and ^{13}C NMR. [c] Products are unknown compounds. All products were characterized by EI-MS, ^{1}H NMR, ^{13}C NMR and HRMS.

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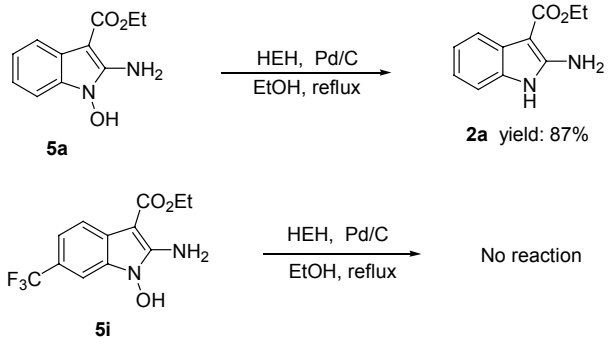
It has been reported the *N*-hydroxy-2-aminoindoles can be reduced to the 2-aminoindole by catalytic hydrogenation under pressure.[4] Similar result was found by refluxing **5a** with HEH in the presence of Pd/C. However, when 2-amino-3-carbethoxy-indoles bear trifluoromethyl group in the phenyl nucleus, the reactions could not proceed at all. For example, *N*-hydroxy-2-aminoindole **5i** was left intact after refluxing with HEH in the presence of Pd/C in ethanol in 10 h (Scheme 3). It may be caused by strong electron-withdrawing ability of trifluoromethyl group which inhibited the reduction.

Scheme 3



The mechanism of selective reduction of nitro group with Hantzsch ester in the presence of Pd/C catalyst has been intensively investigated.[8,9] As illustrated in Scheme 4, the hydrogen atom at the 4-position of HEH was easily transferred in the form of hydride anion in the initial step, which was followed by losing of the hydrogen atom at 1-position. In the present case, HEH acts as reducing agent in a similar way. Based on the above results and literature reports,[8,10] a plausible mechanism could be drawn for this reductive cyclization (Scheme 4). Firstly, 2-cyano-2-(2-nitrophenyl)acetates **1** were reduced to hydroxylamine intermediates **7** by 2 equiv. of HEH. The intermediates **7** could rapidly subject to ring closure to generate *N*-hydroxy-2-aminoindoeles **5**. **7** could also be reduced to aniline intermediates **8** by HEH. Ring closure of **8** onto the cyano group formed the products **2**, and the latter can also be generated by reduction of **5** by HEH. In the present experiments, the reduction of *N*-hydroxy-2-aminoindoeles **5** to 2-aminoindoles **2** was affected by the substituent effects of X and Y as mentioned in Scheme 3. When X and Y are strong electron-withdrawing groups, the transformation did not occur. As a result, both 2-aminoindoles **2** and *N*-hydroxy-2-aminoindoeles **5** formed (Table 2).

Conclusions

In summary, a mild and environmentally benign method for synthesizing 2-aminoindoles have been developed by employing Hantzsch 1,4-dihydropyridine (HEH) as reducing agents. Although the yield was not satisfactory when substrates bear strong electron-withdrawing groups in the phenyl nucleus, it is still the first application of model compounds of coenzyme NAD(P)H in the synthesis of indole derivatives. Extension of this method to other potential substrates and a study of the detailed reaction mechanism are now in progress in our laboratory.

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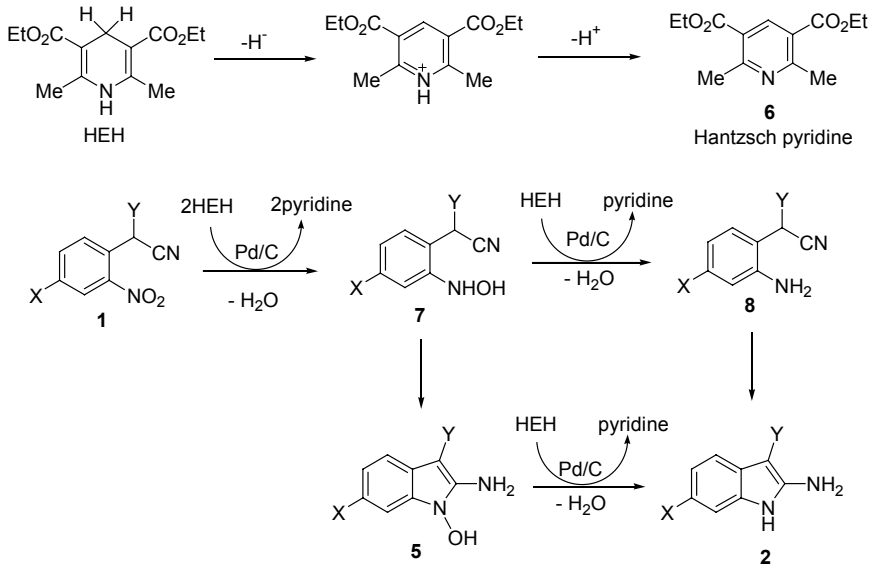
Scheme 4



References

[1] (a) Falkson, C. I.; Ibrahim, J.; Kirkwood, J. M.; Coates, A. S.; Atkins, M. B.; Blum, R. H. *J. Clin. Oncol.* **1998**, *16*, 1743; (b) Viviani, S.; Bonadonna, G.; Santoro, A.; Bonfante, V.; Zanini, M.; Devizzi, L.; Soncini, F.; Valagussa, P. J. *J. Clin. Oncol.* **1996**, *14*, 1421.

[2] (a) Newlands, E. S.; Stevens, M. F. G.; Wedge, S. R.; Wheelhouse, R. T.; Brock, C. *Cancer Treat. Rep.* **1997**, *23*, 35; (b) Bleehen, N. M.; Newlands, E. S.; Lee, S. M.; Thatcher, N.; Selby, P.; Calvert, A. H.; Rustin, G. J. S.; Brampton, M.; Stevens, M. F. G. *J. Clin. Oncol*. **1995**, *13*, 910; (c) Reilly, S. M.; Newlands, E. S.; Glaser, M. G.; Brampton, M.; Rice-Edwards, J. M.; Illinworth, R. D.; Richards, P. G.; Kennard, C.; Colquhoun, I. R.; Lewis, P.; Stevens, M. F. G. *Eur. J. Cancer* **1993**, *29A*, 940; (d) Liang, X.; Pu, X.; Tian, A. *Chin. J. Org. Chem.* **2011**, *31*, 328 (in Chinese).

[3] (a) Forbes, I. T.; Morgan, H. K. A.; Thompson, M. *Synth. Commun*. **1996**, *26*, 745; (b) Munshi, K. L.; Kohl, H.; de Souza, N. J. *J. Heterocycl. Chem*. **1977**, *14*, 1145; (c) Snyder, H. R.; Merica, E. P.; Force, C. G.; White, E. G. *J. Am. Chem. Soc.* **1958**, *80*, 4622.

[4] (a) Belley, M.; Scheigetz, J.; Dubé, P.; Dolman, S. *Synlett* **2001**, 222; for similar reductions, see: (b) Bourdais, J.; Germain, C. *Tetrahedron Lett*. **1970**, *11*, 195, and references cited therein.

[5] Walkington, A.; Gray, M.; Hossner, F.; Kitteringham, J.; Voyle, M. *Synth. Commun*. **2003**, *33*, 2229.

[6] (a) Belley, M.; Sauer, E.; Beaudoin, D.; Duspara, P.; Trimble, L. A.; Dube, P. *Tetrahedron Lett*. **2006**, *47*, 159; (b) Belley, M.; Beaudoin, D.; St-Pierre, G. *Synlett* **2007**, 2999; (c) Belley, M.; Beaudoin, D.; Duspara, P.; Sauer, E.; St-Pierre, G.; Trimble, L. A. *Synlett* **2007**, 2991.

[7] (a) Li, X.; Dong, N.; Cheng, J. *Chem. J. Chin. Univ.* **2012**, *33*, 288 (in Chinese); (b) Hou, S.; Liu, W.; Zhao, Z. *Chin. J. Org. Chem.* **2012**, *32*, 349 (in Chinese).

[8] (a) Shen, X. X.; Liu, Q.; Xing, R. G.; Zhou, B. *Catal. Lett.* **2008**, *126*, 361; (b) Liu, Q.; Li, J.; Shen, X. X.; Xing, R. G.; Yang, J.; Liu, Z. G.; Zhou, B. *Tetrahedron Lett.* **2009**, *50*, 1026; (c) Meng, Q. Y.; Liu, Q.; Li, J.; Xing, R. G.; Shen, X. X.; Zhou, B. *Synlett* **2009**, 3283; (d) Zhao, Y. K.; Liu, Q.; Li, J.; Liu, Z. G.; Zhou, B. *Synlett* **2010**, 1870; (e) Xing, R. G.; Li, Y. N.; Liu, Q.; Meng, Q. Y.; Li, J.; Shen, X. X.; Liu, Z. G.; Zhou, B.; Yao, X. J.; Liu, Z. L. *Eur. J. Org. Chem*. **2010**, 6627; (f) Xing, R. G.; Li, Y. N.; Liu, Q.; Han, Y. F.; Wei, X.; Li, J.; Zhou, B. *Synthesis* **2011**, 2066.

[9] (a) Zhu, X.-Q.; Liu, Y.-C.; Cheng, J.-P. *J. Org. Chem.* **1999**, *64*, 8980; (b) Garden, S. J.; Guimarães, C. R. W.; Corréa, M. B.; Oliveira, C. A. F.; Pinto, A. C.; Alencastro, R. B. *J. Org. Chem.* **2003**, *68*, 8815.

[10] Fukuzumi, S.; Tokuda, Y. *Bull. Chem. Soc. Jpn.* **1992**, *65*, 831.

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