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Highly chemoselective reduction using a Rh/C–Fe(OAc)$_2$ system: practical synthesis of functionalized indoles

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Abstract—Here, we report a highly effective and chemoselective method of preparing substituted indoles from (*E*)-2-nitropyrrolidinostyrenes via hydrogenation in the presence of a rhodium catalyst doped by additives such as $Ni(NO_3)_2{\cdot}6H_2O$, $Fe(OAc)_2$ or $Co(acac)_3$. These hydrogenation conditions may also be applied to other substrates. Aromatic nitro compounds and olefins can be selectively reduced in the presence of aromatic benzyl ethers, aromatic halides and aromatic aldehydes.

The development of DNA topoisomerase I inhibitors as cancer chemotherapy agents is an active area of research.[1] In recent years, the synthesis of indolocarbazole-class DNA topoisomerase inhibitors such as rebeccamycin[2] and arcyriaflavins[3] has attracted widespread interest. We are currently interested in developing an indolocarbazole glycoside DNA topoisomerase I inhibitor (**1**) for this purpose.[4] One of the main issues in its manufacture is the establishment of a practical preparation method for its indole moiety (Fig. 1).

Various methods[5] have been developed for the construction of this ring system. One of the most concise and general methods is the reductive cyclization reaction in which (*E*)-2-nitropyrrolidinostyrenes (**2**) are converted to indoles (**3**) (Scheme 1).[6]

Raney nickel is commonly used as a reagent in the reductive cyclization reaction,[6] but is not suitable for large-scale use due to its pyrophoric nature and potential problems with waste disposal. Reduction with other metals[7] may be considered as an alternative, but this usually results in lower yields compared with Raney nickel reduction, and requires a labour-intensive work-up process to remove metal residues. Catalytic hydrogenation is an alternative high-yielding general method

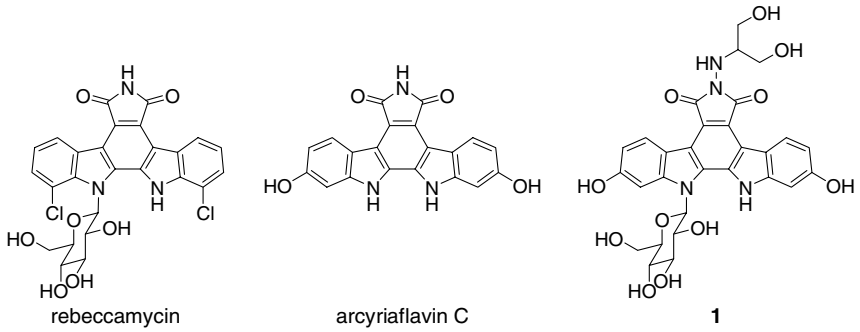

Figure 1. Indolocarbazole drug candidates.

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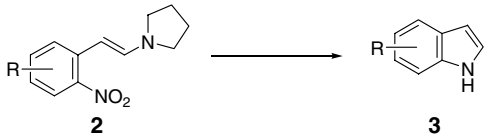
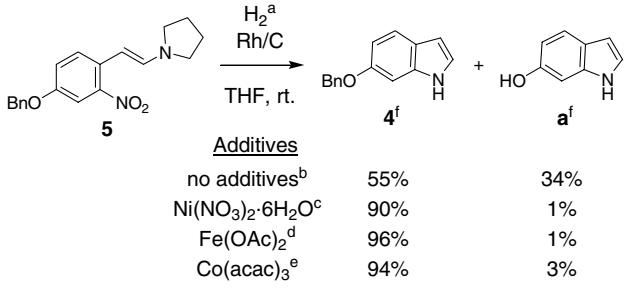


Scheme 1. Reductive cyclization reaction from (*E*)-2-nitropyrrolidinostyrene to indole.

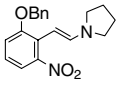
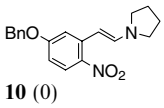
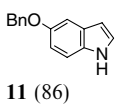
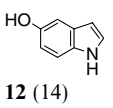
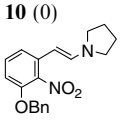
which does not generate stoichiometric amounts of metal waste and can be operated safely. However, chemoselectivity problems such as over-reduction of the indole rings and unwanted reduction of other functional groups (benzyl ethers, aromatic halides, etc.)[8] can sometimes occur. We therefore decided to investigate the conditions for selective catalytic hydrogenation. Here, we report a highly chemoselective, practical method of synthesizing indoles (**3**) via catalytic hydrogenation from (*E*)-2-nitropyrrolidinostyrenes (**2**) in the presence of a catalytic amount of 5% Rh/C with nickel, iron or cobalt salts.

Since 6-benzyloxyindole (**4**) is the key intermediate for our indolocarbazole **1**, the reductive cyclization of enamine (**5**) to the desired indole **4** was the subject of intensive study. As a starting point we examined common catalysts such as Pd/C, Pt/C and Rh/C. Hydrogenation in the presence of Pd/C or Pt/C did not produce the desired indoles and resulted only in over-reduced products.[9] With Rh/C as catalyst, hydrogenation provided a mixture of **4** and de-benzylated indole (**6**). To address the issue of over-reduction, poisoned Pd or Pt catalysts such as Lindler catalyst[8,10] or Pt–sulfide[8,11] were applied, but this mainly resulted in unwanted products.[9,12] Since **6** was the only by-product obtained using the Rh/C catalyst system, we focussed on modification of this system. Doping Rh/C with amines and/or sulfur, which can sometimes poison the platinum group catalysts,[13] did not prevent the de-benzylation reaction. It has been reported that metal cations such as Pb^{4+},[10] Mg^{2+}[14] and Zn^{2+}[15] exhibit poisoning effects.[13,15–17] Several metal salts were screened[18] as modifiers for reduction; the successful results are summarized in Scheme 2. It was found that combinations of Rh/C and $Ni(NO_3)_2{\cdot}6H_2O$, $Fe(OAc)_2$ or $Co(acac)_3$ showed good chemoselectivity and afforded **4** in high yields.[19] In particular, the use



Scheme 2. Reductive cyclization reaction to 6-benzyloxyindole. Reagents and conditions: (a) All reactions were performed under a balloon pressure of hydrogen at room temperature; (b) 3 mol % of 5% Rh/C; (c) 3 mol % of 5% Rh/C with 20 mol % of $Ni(NO_3)_2{\cdot}6H_2O$; (d) 1 mol % of 5% Rh/C with 1 mol % of $Fe(OAc)_2$; (e) 1 mol % of 5% Rh/C with 5 mol % of $Co(acac)_3$; (f) yields were determined by HPLC.

Table 1. Hydrogenation of indoles[a]

Entry	Conditions	Starting materials (%)	Product yields (%)	By-product yields (%)
				
1	Non[e]	**7** (0)	**8** (43)	**9** (38)
2	Ni[b]	**7** (0)	**8** (88)	**9** (6)
3	Fe[c]	**7** (0)	**8** (83)	**9** (5)
4	Co[d]	**7** (0)	**8** (80)	**9** (3)
				
5	Non[e]	**10** (0)	**11** (86)	**12** (14)
6	Ni[b]	**10** (0)	**11** (93)	**12** (1)
7	Fe[c]	**10** (0)	**11** (99)	**12** (1)
8	Co[d]	**10** (0)	**11** (96)	**12** (3)
				
9	Non[e]	**13** (0)	**14** (48)	**15** (52)
10	Ni[b]	**13** (0)	**14** (61)	**15** (0)
11	Fe[c]	**13** (0)	**14** (61)	**15** (0)

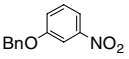
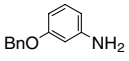
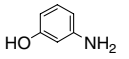
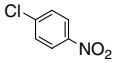
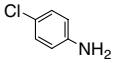
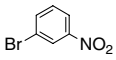
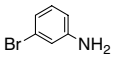
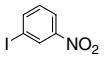
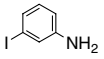
[a] All reactions were performed under a balloon pressure of hydrogen at room temperature. Yields were determined by HPLC after complete conversions.
[b] 3 mol % of 5% Rh/C with 20 mol % of $Ni(NO_3)_2{\cdot}6H_2O$.
[c] 1 mol % of 5% Rh/C with 1 mol % of $Fe(OAc)_2$.
[d] 1 mol % of 5% Rh/C with 5 mol % of $Co(acac)_3$.
[e] 3 mol % of 5% Rh/C.

of $Fe(OAc)_2$ resulted in the isolation of **4** in 96% yield. This method has become one of the cornerstones of the manufacturing process of our drug candidate **1**.

To evaluate the scope and limitations of these hydrogenation reactions, we conducted experiments using other indoles with benzyloxy groups at different positions on the indole ring. The results are summarized in Table 1.[20] The desired indoles were obtained in uniformly high yields without de-benzylation under doping conditions. In general, the 7-substituted indoles were obtained in lower yields than the other substituted indoles due to instability of the 7-subsituted enamine (entries 9–11). The results may reflect a slower reaction under doping conditions than when Rh/C is used by itself.

Chemoselectivity among aromatic nitro groups and other reducible functional groups was examined and the results are summarized in Table 2. In the reactions of 3-benzyloxynitrobenzene (**16**) (entries 1–4), the nitro group was selectively reduced in the presence of the benzyloxy group under the doping conditions. Even when reaction times were prolonged after completion, the formation of 3-hydroxyaniline (**18**) under doping conditions was slower. The iron-doped catalyst (1 mol % of Rh/C) afforded the best result (92% yield) (entry 3), so other substrates were examined extensively under iron-doped conditions. In the reactions of 4-chloronitrobenzene (**19**), the nitro group was reduced in the presence of the chloro group under both no-doping and iron-doping conditions (entries 5 and 6), but the yield was better when the iron additive was used. For 3-bromo- and 3-

Table 2. Hydrogenation of aromatic nitro compounds

Entry	Conditions	Time (h)	Starting materials (%)	Product yields (%)	By-product yields (%)
					
1	Non[a]	15	**16** (0)	**17** (76)	**18** (11)
2	Ni[b]	15	**16** (0)	**17** (92)	**18** (2)
3	Fe[c]	33	**16** (0)	**17** (92)	**18** (1)
4	Co[d]	33	**16** (0)	**17** (89)	**18** (1)
					
5	Non[e]	17	**19** (0)	**20** (78)	**21** (3)
6	Fe[c]	15	**19** (0)	**20** (89)	**21** (4)
					
7	Fe[f]	6	**22** (0)	**23** (86)	**21** (4)
					
8	Fe[g]	3.5	**24** (0)	**25** (86)	**21** (5)

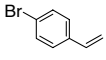
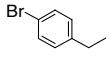
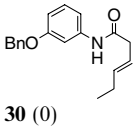
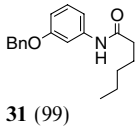
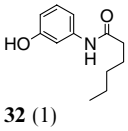
[a] 3 mol % of 5% Rh/C.
[b] 3 mol % of 5% Rh/C with 20 mol % of $Ni(NO_3)_2{\cdot}6H_2O$.
[c] 1 mol % of 5% Rh/C with 1 mol % of $Fe(OAc)_2$.
[d] 1 mol % of 5% Rh/C with 5 mol % of $Co(acac)_3$.
[e] 1 mol % of 5% Rh/C.
[f] The reaction was not completed using 1 mol % of 5% Rh/C and 1 mol % of $Fe(OAc)_2$. 5 mol % of Rh/C and $Fe(OAc)_2$ were used.
[g] The reaction was not completed using 5 mol % of 5% Rh/C and 5 mol % of $Fe(OAc)_2$. 15 mol % of Rh/C and $Fe(OAc)_2$ were used.

iodo-nitrobenzene (**22** and **24**), additional amounts of catalyst were required to complete the reaction (entries 7 and 8).

Iron-doping conditions can also be utilized for selective reduction of aromatic olefins (Table 3, entry 1). Chemoselectivity among olefins, bromo groups and benzyloxy groups was investigated under iron-additive conditions. It was found that the olefin could be cleanly reduced in the presence of bromo and benzyloxy groups (entries 2 and 3). The reduction of aldehyde groups was also investigated. Under the same conditions, the reduction of benzaldehyde in the presence of Rh/C with $Fe(OAc)_2$ was much slower than in the presence of Rh/C alone (entries 4 and 5), which indicates that aromatic aldehyde groups may be tolerated under iron-doped conditions.

In conclusion, we have developed a highly effective and chemoselective method of preparing substituted indoles from (*E*)-2-nitropyrrolidinostyrenes via hydrogenation in the presence of a rhodium catalyst doped by additives such as $Ni(NO_3)_2{\cdot}6H_2O$, $Fe(OAc)_2$ or $Co(acac)_3$. These hydrogenation conditions may also be applied to other substrates. Aromatic nitro compounds and olefins can be cleanly reduced in the presence of aromatic benzyl

Table 3. Hydrogenation of other substrates

Entry	Conditions	Time (h)	Starting materials (%)	Product yield (%)	By-product yield (%)
					
1	Fe[a]	16	**26** (0)	**27** (98)	—
					
2	Fe[a]	2.5	**28** (0)	**29** (100)	**27** (0)
					
3	Fe[a]	3	**30** (0)	**31** (99)	**32** (1)
					
4	Non[b]	16	**33** (17)	—	**34** (56)
5	Fe[a]	16	**33** (86)	—	**34** (7)

[a] 1 mol % of 5% Rh/C with 1 mol % of $Fe(OAc)_2$.
[b] 1 mol % of 5% Rh/C.

ethers, aromatic halides and aromatic aldehydes. This new method has been applied to the industrial-scale production of an intermediate for an anti-cancer drug candidate. We are currently investigating the roles of these doping agents in the reaction mechanism.

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18. Lithium, magnesium, aluminium, zinc, copper, nickel, iron and cobalt salts were screened.
19. Other nickel, iron or cobalt salts ($NiBr_2$, $Ni(acac)_2$, $FeCl_2$, $FeBr_2$, $Fe(OOCCH)_2$, $FeCl_3$, $CoCl_2$, $Co(acac)_2$) also afforded good yields (75–95%); $Ni(NO_3)_2{\cdot}6H_2O$, $Fe(OAc)_2$ and $Co(acac)_3$ were found to provide the best results.
20. General procedure for hydrogenation. To a mixture of enamine **5** (5.00 g, 15.4 mmol), iron(II) acetate (28 mg, 0.154 mmol) and 5% Rh/C (317 mg, 0.154 mmol), tetrahydrofuran (THF) (100 mL) were added. The atmosphere was replaced with N_2, followed by H_2 and continued at room temperature under a balloon pressure of H_2 until the starting enamine **5** and the intermediate 6-benzyloxy-1-hydroxyindole had disappeared. After stirring for 15 h, the atmosphere was replaced with N_2 and aqueous NH_3 (ca. 14%, 20 mL) was added. The following work-up operations were carried out under N_2. After stirring for 20 min, the mixture was filtered to remove the catalyst, which was washed with THF (50 mL). The combined mixture was extracted with toluene (50 mL) and the organic layer was washed with aqueous citric acid (10%, 50 g), aqueous sodium bicarbonate (5%, 50 g) and brine (20%, 50 g). The yield of the target indole **4** was determined by HPLC (3.30 assay g, 96% yield).