Pergamon

Tetrahedron Letters 40 (1999) 8039–8043

TETRAHEDRON
LETTERS

Reduction of the indole ring system: synthesis of 4,5,6,7-tetrahydroindoles

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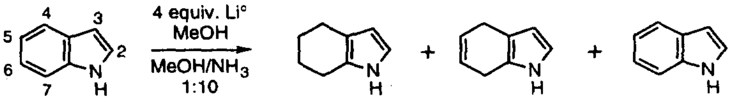
Received 23 August 1999; revised 31 August 1999; accepted 1 September 1999

Abstract

A general two-step procedure for the reduction of indoles to the corresponding 4,5,6,7-tetrahydroindoles has been developed. A regioselective Birch reduction followed by catalytic hydrogenation is employed to accomplish this transformation. Yields for the sensitive pyrrole products are typically between 40 and 50%. This method provides access to complex chiral pyrroles that cannot be readily prepared by other methods. © 1999 Elsevier Science Ltd. All rights reserved.

Keywords: pyrroles; indoles; reduction; alkaloids.

Pyrrole rings are important components of many biologically active natural products[1–3] and can be used as η^5 ligands for transition metals.[4–9] In the context of transition metals 4,5,6,7-tetrahydroindoles (cyclohexeno[2,3-*a*]pyrroles) are interesting because they are isoelectronic with the corresponding tetrahydroindenyl ligands. While η^5 coordination of indenyl ligands makes them easy to hydrogenate, η^5 coordination of indolyl ligands is difficult to achieve relative to η^1 coordination with the indole nitrogen. Consequently, 4,5,6,7-tetrahydroindoles must be synthesized prior to η^5 metal coordination. Alkylpyrroles are highly reactive and can be difficult to synthesize directly. In contrast, indoles are less reactive, easy to synthesize, and can be reduced under dissolving metal conditions.[10–12] While the dissolving metal reduction of indole has been shown to give primarily 4,7-dihydroindole **3**, these sensitive products have not been further reduced to the 4,5,6,7-tetrahydroindoles.



1 **2** **3** ***sm*** (1)

There are two challenges associated with the Birch reduction of indoles to the 4,5,6,7-tetrahydroindoles. The first challenge is to prevent the buildup of unreactive indolyl anion formed

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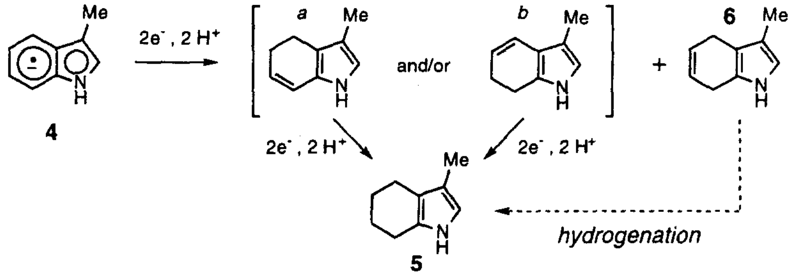
PII: S0040-4039(99)01687-1

under the basic reaction conditions. Birch reduction in the presence of methanol has been shown to reduce the amount of recovered starting material (Eq. 1).[10] However, complete consumption of the starting material is essential, because the starting material is not easily separated from the desired tetrahydroindole **2**. The second challenge is to complete the reduction of 4,7-dihydroindole **3** by hydrogenation of the sensitive product mixture.

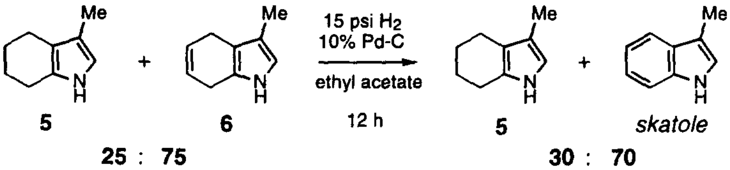
For the reduction of skatole (3-methylindole), addition of increasing proportions of methanol (up to 20%) failed to consume the starting material. In an effort to reduce the basicity of the reaction medium, 5 equiv. ammonium chloride was added in a single portion 5 min after addition of the lithium metal. Under these conditions, the starting material is completely consumed. This important modification obviates the need to separate skatole from the final product mixture.

The ratio of tetrahydroskatole **5** and dihydroskatole **6** is typically between 1:2 and 1:3. As shown in Scheme 1 the ratio of **5** and **6** is determined by the protonation of the radical anion intermediates to give reactive dihydroskatole **a** and/or **b**, or unreactive dihydroskatole **3a**. It is difficult to control these protonation steps, especially since relatively acidic conditions are required for complete consumption of the starting indole. Instead, a second hydrogenation step was used to convert dihydroskatole **6** into tetrahydroskatole **5** without prior separation.



Scheme 1.

The catalytic hydrogenation of dihydroskatole **6** is complicated by its propensity to re-aromatize. This oxidative process, related to transfer hydrogenation,[13] is pronounced when Pd-C is used as the catalyst at atmospheric pressure (Eq. 2). Reoxidation is still a problem when 1,4-cyclohexadiene is used as the hydrogen source.

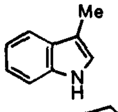
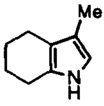
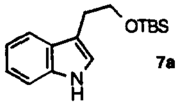
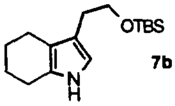
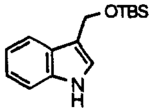
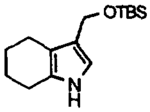
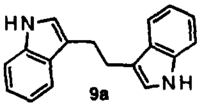
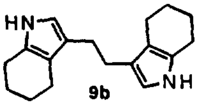
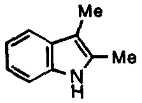
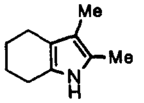
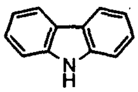
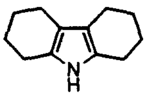


(2)

Better results were obtained with rhodium- and platinum-based catalysts under 50 psi hydrogen. While Rh/Al_2O_3 gave good results with 3-substituted indoles **7b**–**9b**, Wilkinson's catalyst (under 1 atm hydrogen) gave better results with 2,3-disubstituted indoles. In general, yields for the two-step reduction of indoles to tetrahydroindoles are generally within the range of 40–50% (Table 1), even when the substrate contained more than one aromatic ring. These yields are consistent with the extraordinary sensitivity of alkylpyrroles to oxidative oligomerization[14] and autoxidation.[15,16] The best yield was obtained for 2,3-dimethyl-4,5,6,7-tetrahydroindole, which was purified by distillation.

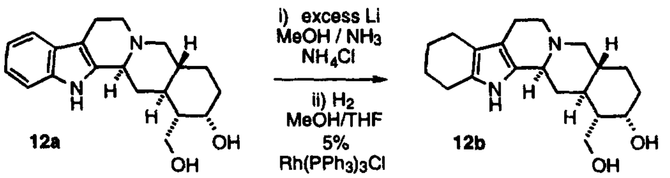
Knorr-type condensation approaches work well for the synthesis of simple pyrroles, especially pyrroles with electron-withdrawing groups.[17] However, the two-step reduction of indoles makes chiral pyrroles available from the chiral pool of alkaloids. For example, reduction of yohimbinol[18] gives the correspon-

Table 1
Two-step reduction of indoles to tetrahydroindoles

indole	tetrahydroindole	hydrogenation catalyst	mol% catalyst	solvent	YIELD (2 steps)
	 5	5% Rh/Al_2O_3	10	DMF	48%[a]
		10% Pt-C	5	EtOAc	50%[a]
 7a	 7b	5% Rh/Al_2O_3	10	DMF	40%
		10% Pt-C	5	EtOAc	35%
 8a	 8b	5% Rh/Al_2O_3	10	DMF	23%
 9a	 9b	5% Rh/Al_2O_3	10	DMF	44%
 10a	 10b	$(Ph_3P)_3RhCl$	2	2:1 MeOH/THF	68%[a]
 11a	 11b	$(Ph_3P)_3RhCl$	5	2:1 MeOH/THF	55%

a. purified by distillation

ding pyrrole **12b**[19] in yields comparable to those obtained for the simple indoles in Table 1. Pyrrole **12b** associates strongly with ethanol and oxygen.[20,21] Following chromatographic purification of **12b** with methanol/chloroform, 0.5 equiv. ethanol is retained from the eluent. In addition, ^1H NMR samples of **12b** in chloroform must be degassed (freeze/pump/thaw) to remove oxygen that leads to selective signal broadening.



48% (3)

In summary, a general two-step procedure for the reduction of indoles to the corresponding 4,5,6,7-tetrahydroindoles has been developed. This procedure involves Birch reduction followed by catalytic hydrogenation. This method provides access to complex chiral pyrroles that cannot be readily prepared by other methods.

1. Typical procedure: reduction of skatole to tetrahydroindole 5

A dry three-neck flask was charged with 75 mL of liquid ammonia at −78°C. Methanol (15 mL) was added followed by the skatole (0.26 g, 2.0 mmol). Lithium metal (0.21 g, 30 mmol) was added and the mixture was stirred for 5 min leading to a blue solution. After 5 min, NH_4Cl (0.53 g, 10 mmol) was added and stirring was continued for 30 min at −78°C. Over the next hour about half of the ammonia was allowed to boil off and the mixture was then carefully poured into water and the aqueous solution was extracted three times with Et_2O. The combined organic layers were washed with water and brine, and then dried over $MgSO_4$. Filtration and concentration of the solvent in vacuo provided a mixture of 4,7-dihydroskatole and 4,5,6,7-tetrahydroskatole (0.25 g) as an off-white solid. The air sensitive product mixture was used immediately in the hydrogenation step without further purification.

The mixture of partially reduced skatole was added to 10% Pt-C (0.19 g, 0.1 mmol) in 50 mL ethyl acetate and the reaction mixture was stirred under 50 psi hydrogen for 12 h. After this time the mixture was diluted with ethyl acetate and filtered through Celite. Concentration of the solvent in vacuo provided the crude product. Kugelrohr distillation afforded pyrrole **5** (0.14 g, 50%) as white crystalline solid that is air sensitive. Non-volatile pyrroles **7b**–**12b** were purified by silica gel chromotagraphy.

Acknowledgements

This work was supported by the National Science Foundation (CHE-9623903) with additional support from the Glaxo-Wellcome Chemistry Scholars program, Eli Lilly, Dupont, the Camille and Henry Dreyfus Foundation, and the Petroleum Research Fund.

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19. (a) Bis-pyrrole **9b**: mp 157–158°C (acetonitrile); R_f=0.57 (20% ethyl acetate/hexane; Al_2O_3); IR (KBr) 3366, 1589, 1517 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ: 7.52 (br s, 2H), 6.48 (d, *J*=2.1 Hz, 2H), 2.64 (s, 4H), 2.56 (m, 4H), 2.48 (m, 4H), 1.79 (m, 8H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 127.0, 122.6, 116.2, 112.3, 26.6, 23.7, 23.3, 22.9, 21.4; LRMS (CI) *m/z* (relative intensity): 268 (65), 147 (45), 134 (100); HRMS (CI): *m/z*: calcd for $C_{18}H_{24}N_2$ (M^+): 268.1939; found: 268.1938. (b) Tetrahydroyohimbinol **12b**: mp 176–180°C dec ($CHCl_3$); R_f=0.16 (10% MeOH/$CHCl_3$); IR (KBr) 2851, 2756 cm^{-1};

^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.74 (br s, 1H), 4.29 (d, J=2.4 Hz, 1H), 3.99 (dd, J=11.2, 4.0 Hz, 1H), 3.89 (dd, J=11.2, 1.8 Hz, 1H), 3.18 (d, J=11.0 Hz, 1H), 2.96 (dd, J=11.2, 5.7 Hz, 1H), 2.89 (dd, J=11.0, 3.3 Hz, 1H), 2.72 (m, 1H), 2.55 (m, 2H), 2.52 (td, J=11.2, 4.0 Hz, 1H), 2.38 (m, 3H), 2.25 (dt, J=12.3, 1.0 Hz, 1H), 2.18 (t, J=10.7 Hz, 1H), 1.91–1.73 (m, 7H), 1.70–1.41 (m, 5H), 1.34 (m, 1H), 1.22 (q, J=11.8 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 126.4, 125.6, 114.9, 112.7, 72.3, 63.8, 61.7, 60.4, 53.5, 46.3, 41.4, 34.8, 33.7, 33.3, 24.1, 23.6, 23.5, 22.8, 22.0, 21.1; LRMS (CI) *m/z* (relative intensity): 330 (100), 313 (45), 188 (35); HRMS (CI): *m/z* calcd for $C_{20}H_{30}N_2O_2$ (M^+): 330.2307; found: 330.2319.

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