Palladium-Catalyzed Reduction of *N*-(*tert*-Butoxycarbonyl)indoles by Polymethylhydrosiloxane[1]

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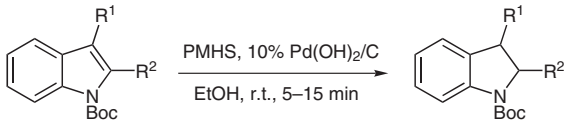
Abstract: The palladium-catalyzed [10% $Pd(OH)_2$/C] reduction of *N*-(*tert*-butoxycarbonyl)indoles to the corresponding *N*-(*tert*-butoxycarbonyl)indolines is described. Polymethylhydrosiloxane was used as reducing agent and the reaction proceeded smoothly at room temperature in short reaction times giving the products in good yields.

Key words: palladium catalysis, reduction, indoles, polymethylhydrosiloxane

The reduction of indoles to indolines is a commonly encountered reaction and a number of methods have been developed for this conversion, including those involving hydrogenation and hydride reductions.[2] The reagents used for this transformation have been sodium borohydride or sodium cyanoborohydride in carboxylic acids,[3] zinc borohydride,[4] magnesium in methanol,[5] triethylsilane/trifluoroacetic acid,[6] borane–pyridine in hydrogen chloride,[7] and hydrogen over catalysts,[8] amongst others.[9] While several of these methods have seen wide use, chemists continue to seek new protocols using safer reducing agents. Silanes and siloxanes have been identified as alternative and safe reducing agents when compared to conventional reduction procedures.[10] In particular, polymethylhydrosiloxane (PMHS) is gaining prominence as an inexpensive reagent and is an air- and moisture-stable reducing agent.[11] Indeed, polymethylhydrosiloxane can be stored for longer periods of time, and no special precautions are needed when this reagent is used. Recent studies of polymethylhydrosiloxane as a reducing agent by us[12] and others[13] suggest that additional opportunities may exist for its use in indole reductions.

Accordingly, polymethylhydrosiloxane was used as an efficient reducing agent for the reduction of *N*-Boc-protected indoles to *N*-Boc-protected indolines in the presence of 10% palladium(II) hydroxide on carbon as a catalyst (Scheme 1).



Scheme 1

Initially, *N*-(*tert*-butoxycarbonyl)indole and polymethylhydrosiloxane were stirred in the presence of different potential activators such as tris(pentafluorophenyl)borane, zinc(II) chloride, aluminum trichloride, tetrakis(triphenylphosphine)palladium, and palladium on carbon (Table 1), but, to our disappointment, either no or hardly any *N*-(*tert*-butoxycarbonyl)indoline formed (Table 1, entries 1, 2, 4) or it formed in 60–80% yield only (entries 3, 5). A more careful study resulted in the identification of 10% palladium(II) hydroxide on carbon as an efficient activator for the reduction of *N*-Boc-indoles. Thus, the reaction of *N*-(*tert*-butoxycarbonyl)indole with polymethylhydrosiloxane in the presence of a catalytic amount of 10% palladium(II) hydroxide on carbon in ethanol gave the corresponding indoline product in 96% yield (Table 1, entry 6).

Table 1 Reduction of *N*-(*tert*-Butoxycarbonyl)indole with Polymethylhydrosiloxane in the Presence of Different Catalysts

Entry	Catalyst	Time (h)	Yield (%)
1	$B(C_6F_5)_3$	12	no reaction
2	$ZnCl_2$	18	10
3	$AlCl_3$	18	60
4	$Pd(PPh_3)_4$	12	no reaction
5	10% Pd/C	2	80
6	10% $Pd(OH)_2$	0.1	96

To explore the scope of the reaction, various *N*-Boc-indoles (Table 2, entries 1–8, 10, 11) were treated under the reaction conditions described above to give the corresponding *N*-Boc-indolines in good yields. In all these cases, the reaction proceeded smoothly at room temperature in 5–15 minutes (Table 2). The ester functionality is stable (Table 2, entries 6, 8, 9) and, as expected, the carbonyl and nitro functionalities were reduced (entries 4, 7, 11) under these reaction conditions. The reduction of *N*-acetylindole **9a** was also achieved, giving the corresponding indoline **9b** in five minutes in 93% yield (Table 2, entry 9). *N*-Benzylindole (**12a**) did not change under the described reduction conditions, which resulted in debenzylation to give the indole; instead, **12a** was reduced with a polymethylhydrosiloxane/aluminum trichloride system to give *N*-benzylindoline (**12b**) in 85% yield (Table 2, entry 12). However, *N*-sulfonylindole **13a** failed to give the

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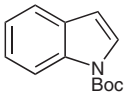
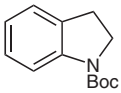
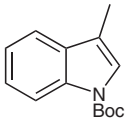
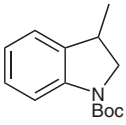
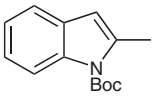
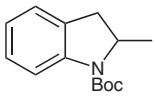
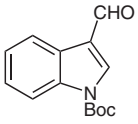
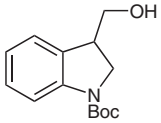
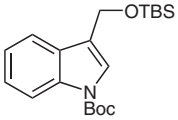
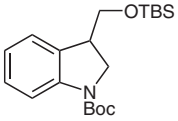
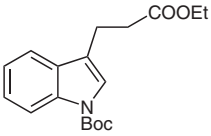
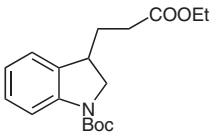
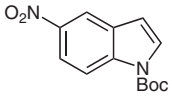
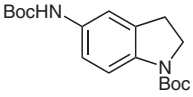
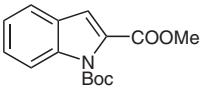
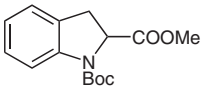
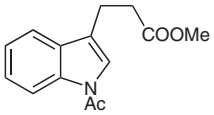
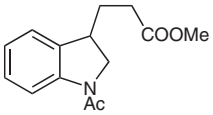
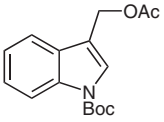
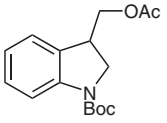
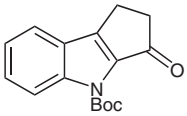
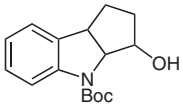
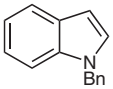
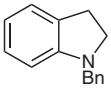
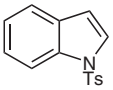
Table 2 Reduction of *N*-Boc-Protected Indole Derivatives by Polymethylhydrosiloxane in the Presence of 10% Palladium(II) Hydroxide on Carbon

Entry	Indole		Time (min)	Indoline		Yield[a] (%)
1		**1a**	5		**1b**	96[8b]
2		**2a**	10		**2b**	92[8b]
3		**3a**	10		**3b**	90[8b]
4		**4a**	15		**4b**	85[14]
5		**5a**	15		**5b**	88
6		**6a**	10		**6b**	92
7[b]		**7a**	10		**7b**	86
8		**8a**	5		**8b**	88[8b]
9		**9a**	10		**9b**	93
10		**10a**	10		**10b**	87
11		**11a**	10		**11b**	82
12[c]		**12a**	120		**12b**	85[15]
13		**13a**	120	no reaction	–	–

[a] Isolated yields after purification by column chromatography. The literature references are given for the known products.
[b] After completion of the reduction, the reaction mixture was treated with Boc_2O.
[c] $AlCl_3$ was used as the catalyst, while in all other entries $Pd(OH)_2$ was used.

corresponding indoline in the presence of polymethylhydrosiloxane with either 10% palladium(II) hydroxide on carbon or aluminum trichloride (Table 2, entry 13).

In summary, we have demonstrated a useful method for the reduction of *N*-Boc-indoles to the corresponding indolines using polymethylhydrosiloxane as a safe reducing agent in the presence of a catalytic amount of 10% palladium(II) hydroxide on carbon. We believe this method is a useful addition to the existing protocols and may find application in organic synthesis.

^{1}H (300 MHz) and ^{13}C (75 MHz) NMR spectra of samples in $CDCl_3$ were recorded on a Bruker Avance 300 spectrometer. ESI-MS determinations were carried out on an Agilent Technologies LC/MSD trap SL spectrometer. Column chromatography was performed on silica gel (Merck, 100–200 mesh). EtOH was dried over sodium cake, EtOAc and hexanes (LR grade) were used as received commercially. The *N*-Boc indoles were obtained trough standard proceedures using Boc_2O. PMHS and $Pd(OH)_2$/C were obtained from Aldrich and used as received.

Indolines 1b–12b; General Procedure

PMHS (180 mg, 3 mmol) was added to a stirred soln of one of indoles **1a**–**12a** (1 mmol) in anhyd EtOH (5 mL). The mixture was cooled to 0 °C and 10% $Pd(OH)_2$/C (10 mg) was added. The mixture was stirred vigorously for 5 min and, after completion of the reaction (monitored by TLC), the mixture was filtered through a pad of Celite. Volatiles were removed on a rotary evaporator, and the residue was purified by subsequent column chromatography (silica gel, EtOAc–hexane); this gave the corresponding indoline.

***tert*-Butyl 3-[(*tert*-Butyldimethylsiloxy)methyl]indoline-1-carboxylate (5b)**

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.81 (br s, 1 H), 7.18–7.04 (m, 2 H), 6.92–6.85 (m, 1 H), 4.10–3.95 (m, 1 H), 3.94–3.70 (m, 1 H), 3.58–3.30 (m, 3 H), 1.56 (s, 9 H), 0.85 (s, 9 H), 0.08 (s, 6 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 152.5, 128.1, 127.5, 122.2, 121.98, 114.7, 114.6, 66.2, 55.6, 51.1, 28.4, 25.8, 20.2, 18.2, –5.3.

ESI-MS: *m*/*z* = 386 [M^+ + Na].

***tert*-Butyl 3-(3-Ethoxy-3-oxopropyl)indoline-1-carboxylate (6b)**

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.84 (br s, 1 H), 7.2–7.12 (m, 2 H), 6.96–6.91 (m, 1 H), 4.13 (q, *J* = 7.55 Hz, 2 H), 4.05 (m, 1 H), 3.70–3.60 (m, 1 H), 3.40–3.30 (m, 1 H), 2.36 (t, *J* = 6.79 Hz, 2 H), 2.16–2.06 (m, 1 H), 1.95–1.82 (m, 1 H), 1.56 (s, 9 H), 1.28 (t, *J* = 7.55 Hz, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 173.1, 152.2, 133.2, 127.9, 125.5, 124.1, 122.2, 114.7, 81.8, 60.5, 53.3, 38.5, 31.4, 30.3, 28.4, 14.2.

ESI-MS: *m*/*z* = 342 [M^+ + Na].

***tert*-Butyl 5-[(*tert*-Butoxycarbonyl)amino]indoline-1-carboxylate (7b)**

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.46–7.32 (m, 1 H), 6.89–6.79 (m, 1 H), 6.30 (s, 1 H), 3.96 (t, *J* = 6.57 Hz, 2 H), 3.08 (t, *J* = 6.57 Hz, 2 H), 1.48 (br s, 18 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 152.6, 151.7, 133.0, 117.6, 115.6, 114.6, 79.8, 79.8, 57.6, 47.6, 29.7, 28.5, 28.4, 28.0, 18.1.

ESI-MS: *m*/*z* = 357 [M^+ + Na].

Methyl 3-(1-Acetylindolin-3-yl)propanoate (9b)

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.12 (d, *J* = 7.55 Hz, 1 H), 7.24–7.12 (m, 2 H), 7.02–6.96 (m, 1 H), 4.20–4.14 (m, 1 H), 3.65 (s, 3 H), 3.48–3.40 (m, 1 H), 3.02–2.98 (m, 1 H), 2.45 (t, *J* = 6.74 Hz, 2 H), 2.21 (s, 3 H), 2.18–2.06 (m, 1 H), 1.96–188 (m, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 172.7, 168.0, 142.6, 133.5, 128.1, 123.7, 123.5, 117.1, 54.6, 51.5, 39.1, 30.9, 30.2, 23.9.

ESI-MS: *m*/*z* = 270 [M^+ + Na].

***tert*-Butyl 3-(Acetoxymethyl)indoline-1-carboxylate (10b)**

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.70 (br s, 1 H), 7.10–7.01 (m, 2 H), 6.82–6.78 (m, 1 H), 4.16–4.10 (m, 1 H), 3.98–3.88 (m, 2 H), 3.70–3.60 (m, 1 H), 3.52–3.40 (m, 1 H), 1.94 (s, 3 H), 1.45 (s, 9 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 170.9, 152.5, 128.5, 124.6, 122.2, 114.9, 80.8, 66.5, 51.2, 39.2, 28.4, 20.8.

ESI-MS: *m*/*z* = 314 [M^+ + Na].

***tert*-Butyl 3-Hydroxy-2,3,3a,8b-tetrahydrocyclopenta[*b*]indole-4(1*H*)-carboxylate (11b)**

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.40 (br s, 1 H), 7.04–6.95 (m, 2 H), 6.82–6.78 (m, 1 H), 4.58–4.52 (m, 1 H), 4.26–4.19 (m, 1 H), 3.73–3.66 (m, 1 H), 1.98–1.88 (m, 2 H), 1.76–1.67 (m, 2 H), 1.50 (s, 9 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 152.2, 143.4, 135.2, 127.5, 124.0, 122.9, 114.9, 81.8, 76.5, 64.9, 43.5, 29.4, 29.1, 28.4, 20.6.

ESI-MS: *m*/*z* = 298 [M^+ + Na].

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