SYNTHESIS OF NITROETHYLINDOLES FROM NITROVINYLINDOLES BY ALKOXYBOROHYDRIDE REDUCTION

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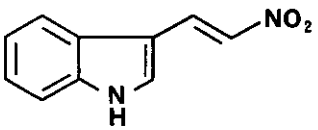
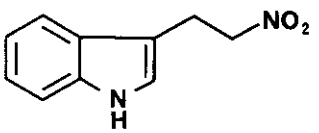
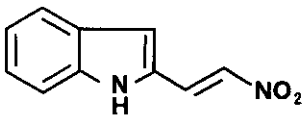
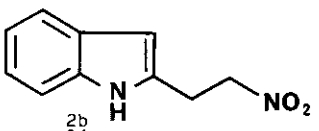
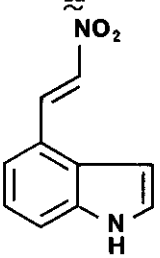
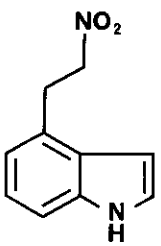
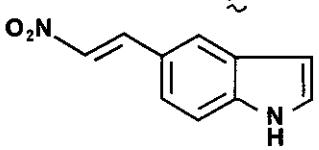
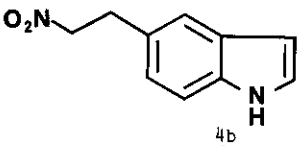
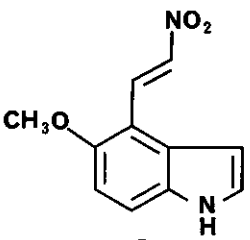
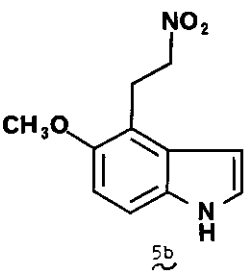
Abstract - The reduction of substituted nitrovinylindoles to the corresponding nitroethylindoles proceeds in excellent yield, with the suppression of dimeric Michael byproducts, when an alkoxyborohydride is the reducing agent. A study of the reaction demonstrates the equivalence of preformed sodium trimethoxyborohydride and alkoxyborohydride generated *in situ* from excess sodium borohydride and methanol.

Substituted nitroethylindoles have proven valuable as intermediates in the synthesis of functionalized polycyclic indoles and natural products of the ergoline class.[1] Nitroalkylindoles have been prepared from quaternary gramine salts,[2] by the displacement of gramines activated *in situ*,[3] by Michael addition of nitromethane to unsaturated carbonyls,[1c,f] and more recently, by the direct nitroethylation of the indole 3 position.[4]

During a study of rigid 5-hydroxytryptamine derivatives[5] we required various substituted nitroethylindoles, *e.g.* 2b-5b, which are inaccessible *via* known procedures. Nitrovinylindoles, 1a-5a (Table I), are obvious precursors to the corresponding saturated compounds, since only a change in oxidation state is required. Unfortunately, catalytic hydrogenation,[6] sodium borohydride (with or without buffer),[7] or sodium cyanoborohydride[8] all proved ineffective, producing either low yields of product or complex mixtures. In particular, sodium borohydride is reported to be unsatisfactory when applied to the reduction of nitrovinylindole,[7c] a result that we confirmed in multiple experiments with 1a. During experiments with this reducing agent, however, a surprising solvent effect was observed (Table II). While reduction of 1a with sodium borohydride in 2-propanol afforded 1b and Michael dimer 1c in a 2:1 ratio, the use of ethanol, or better, methanol, as the solvent markedly increased the ratio of 1b to 1c.

Formation of dimer 1c by Michael reaction of 1b (present in the basic reaction mixture as nitronate anion) with starting nitroolefin 1a competes with conjugate reduction of 1a to 1b. Accelerating the reduction step would therefore be expected to increase the ratio of 1b to 1c. The

Table I. Reduction of Substituted Nitrovinylindoles with $NaBH_4$/MeOH

Entry	Structure	Product[14]	% Yield[a]
1			79
	1a	1b	
2			98
	2a	2b	
3			74
	3a	3b	
4			71
	4a	4b	
5			91
	5a	5b	

[a] Yields are for isolated pure materials.

vigorous reaction of sodium borohydride with methanol, and prior observations[9] implicating sodium borohydride/methanol mixtures or preformed alkoxyborohydrides to be more powerful reducing agents than sodium borohydride alone, led us to suspect an incipient alkoxyborohydride as the reducing agent in the present reaction. This line of reasoning was supported by Experiment 5 (Table II), where sodium trimethoxyborohydride/2-propanol reproduced the product ratio obtained with sodium borohydride/methanol.[10] When tetrahydrofuran, an aprotic solvent, was used the ratio of 1b:1c increased to >35:1 (Table II, Experiment 6) but the yield of 1b remained constant due to the formation of small amounts of several unidentified byproducts.

Application of the sodium borohydride/methanol reduction to a variety of nitrovinylindoles provides good to excellent yields of nitroalkylindoles (Table I) in a procedure which is easily performed on a preparative scale (Illustrative Experiment). This reduction coupled with the ready availability of nitrovinylindoles from condensation of indolecarboxaldehydes with nitromethane[11] or direct nitrovinylation of the indole ring[12] provides a simple and convenient access to a variety of substituted nitroethylindoles.

An attempt to reduce nitrostyrene with sodium trimethoxyborohydride/tetrahydrofuran produced an inferior yield (20%) of nitroethylbenzene. This result suggests the present method may be limited to substituted indoles and therefore complements the method recently described by Borchardt[13] for the reduction of substituted nitrostyrenes to nitroethylbenzenes.

ILLUSTRATIVE EXPERIMENT: 5-Methoxy-4-(2-nitroethyl)-1H indole (5b).

A mixture of indole 5a (9.1 g, 41.7 mmole) and methanol (420 mL) was stirred during the portionwise addition (20 min) of sodium borohydride (7.0 g, 185 mmole, 4.4 eq.). The solution was sitrred for 20 min after the addition of sodium borohydride was completed, then adjusted to pH 6 with acetic acid (ca. 15 ml), and concentrated. The residue was diluted with water and extracted three times with ethyl acetate. The ethyl acetate extracts were combined, washed with water, dried (brine, Na_2SO_4) and concentrated. Flash chromatography[15] of the solid product with 40% ethyl acetate-hexane as eluant yielded 8.38 g (91%) of 5b as light yellow crystals: mp 80-81°.[14]

Anal. Calcd. for $C_{11}H_{12}N_2O_3$: C, 59.99; H, 5.49; N, 12.72.
Found: C, 60.04; H, 5.50; N, 12.62.

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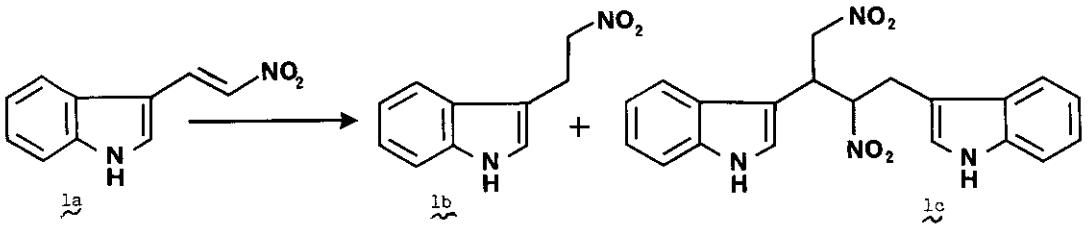
Table II. Reduction of 3-Nitrovinylindole



Experiment	Conditions[a]	Product Ratio[b] 1b : 1c	% Yield 1b [c]
1	$NaBH_4$/2-PrOH	2:1	51
2	$NaBH_4$/1:1 2-PrOH:THF	3:1	58
3	$NaBH_4$/EtOH	8:1	62
4	$NaBH_4$/MeOH	12:1	79
5	$NaBH(OCH_3)_3$/2-PrOH	14:1	83
6	$NaBH(OCH_3)_3$/THF	>35:1	87

[a] Reducing agent (10.6 mmole) was added (1-5 min) to a solution or suspension of 1a (200 mg, 1.06 mmole) in the stated solvent (10 ml).

[b] Determined from isolated yields of 1b and 1c.

[c] Isolated yield of pure product.

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13. A.K. Sinhababu and R.T. Borchardt, Tetrahedron Lett., 1983, 227. It is interesting to note that the silica gel assisted reduction of nitrovinylbenzenes described by these authors demonstrates a reversed preference for solvent, such that 2-propanol is more effective than methanol or ethanol for suppressing dimer formation. The mechanistic implications of this result are at present unclear.
14. Spectroscopic data for compounds 1b-5b: (1b) ir (Nujol mull) 3400, 1550 cm^{-1}; nmr ($CDCl_3$) δ 3.5 (t, J=7 Hz, 2H), 4.68 (t, J=7 Hz, 2H), 6.8-7.6 (br m, 5H), 7.8-8.3 (br s, 1H); (2b) ir (neat melt) 3400, 1560 cm^{-1}; nmr ($CDCl_3$)δ 3.2 (t, J=7 Hz, 2H), 4.5 (t, J=7 Hz, 2H), 6.2 (br s, 1H), 6.9-7.3 (br m, 3H), 7.5 (m, 1H), 7.7-8.0 (br s, 1H); (3b) ir (Nujol mull) 3420, 1550, 1540 cm^{-1}; nmr ($CDCl_3$)δ 3.52 (t, J=7 Hz, 2H), 4.68 (t, J=7 Hz, 2H), 6.5 (br s, 1H), 6.8-7.3 (m, 4H), 8.0-8.4 (br s, 1H); (4b) ir (neat) 3400, 1550, 1530 cm^{-1}; nmr ($CDCl_3$)δ 3.3 (t, J=7 Hz, 2H), 4.52 (t, J=7 Hz, 2H), 6.5 (m, 1H), 6.9 (dd, J=2 Hz, 9Hz, 1H), 7.1 (t, J=3 Hz, 1H) 7.25 (d, J=9 Hz, 1H), 7.42 (br s, 1H), 7.8-8.3 (br s, 1H); (5b) ir (nujol mull) 3420, 1580, 1540, 1380 cm^{-1}; nmr ($CDCl_3$)δ 3.55 (t, J=7 Hz, 2H), 3.83 (s, 3H), 4.63 (t, J=7 Hz, 2H), 6.46 (br s, 1H) 6.8 (d, J=8 Hz, 1H), 7.1-7.3 (m, 2H), 8.0-8.3 (br s, 1H).
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