siderations usually restricted initial concentrations of iodide salts to no more than 6 times the initial ether concentration for the most concentrated ether solutions used in the kinetic runs. For preparative scale cleavage reactions no problems were encountered when the iodide salts were not completely soluble at the start of the reaction.

In the small scale reactions (2–8 mmol of ether) used to determine the kinetic rate constants, changes in the concentration of ethers and products with time were followed by analyzing aliquots by HPLC for compounds **1**, **2**, **3**, and **6** or by quantitative proton NMR in $CDCl_3$ using 1-methylnaphthalene as the internal standard for compounds **1a**, **4**, **5**, **7**, **8**, and **9**. HPLC is more accurate and precise but requires tedious sample preparation in order to separate the analytes from iodide salts and solvent pyridine prior to injection onto the column. Quantitative NMR is less precise but requires no sample preparation. Rate constants for **1a** determined by both methods agreed within experimental error. For the HPLC analyses, aliquots were quenched in aqueous H_2SO_4, extracted with 1,2-dichloroethane, dried, diluted with acetonitrile, and concentrated on a C_{18} Sep-Pak cartridge (Waters) prior to analysis on a C_{18} reverse-phase analytical column using an $CH_3CN/H_2O/HOAc$ (23/75/2) mobile phase. Pseudo-first-order rate constants (k, s^{-1}) were calculated from the slope of a least-squares fit of ln $[C/C_0]$ vs. time data taken through at least 4 half-lives. Rate constant values reported in the table are averages of two or three reactions.

Acknowledgment. We thank the Illinois Coal Development Board and the Faculty Research Council of Eastern Illinois University for financial support and Kenneth Osborne, Linda Warfel, and Milind Vaidya for laboratory assistance during various phases of this study.

Registry No. **1a**, 579-75-9; **1b**, 134-11-2; **1c**, 2243-42-7; **2**, 100-09-4; **3**, 606-45-1; **4a**, 3588-75-8; **4b**, 104422-22-2; **5a**, 10075-66-8; **5b**, 104422-23-3; **6a**, 90-05-1; **6b**, 6272-38-4; **7**, 5635-98-3; **8**, 21998-86-7; **9**, 612-16-8.

Supplementary Material Available: Analytical and spectroscopic data for compounds **4a,b**, **5a,b**, **7**, **8**, **13**, **14**, and py–HI (3 pages). Ordering information is given on any current masthead page.

Nickel Boride/Hydrazine Hydrate: Reduction of Aromatic and Aliphatic Nitro Compounds. Synthesis of 4-(Benzyloxy)indole and α-Alkyltryptamines

David H. Lloyd and David E. Nichols*

Department of Medicinal Chemistry and Pharmacognosy, School of Pharmacy and Pharmacal Sciences, Purdue University, West Lafayette, Indiana 47907

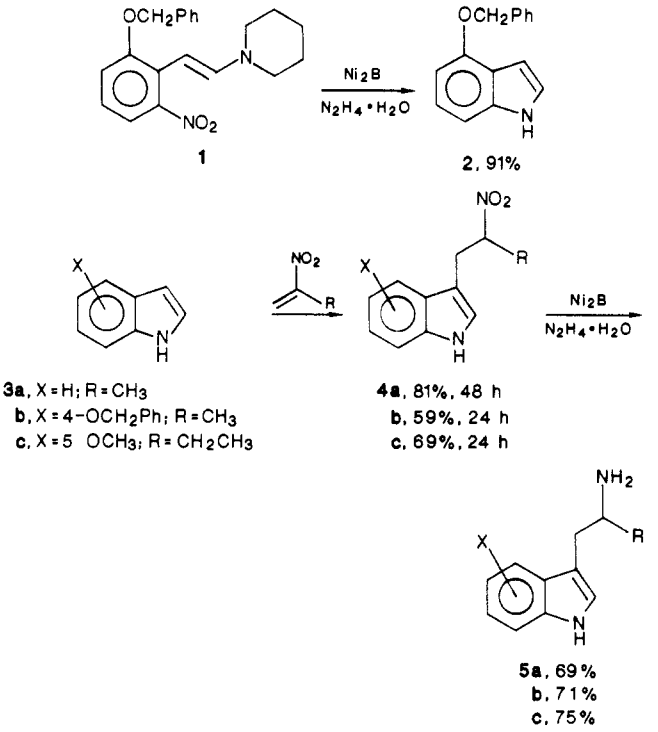
Received February 24, 1986

In the context of our ongoing research, it became necessary to prepare quantities of 4-, 5-, or 6-alkoxyindoles. We had developed a two-step synthesis from *o*-nitrotoluenes as a simplified variation of the Leimgruber and Batcho method.[1] For example, 2-(benzyloxy)-6-nitrotoluene was reacted with tripiperidinomethane (TPM) and the resulting nitropiperidinostyrene **1** was reduced with aqueous titanous chloride to provide 4-(benzyloxy)indole (**2**) in 65% overall yield.[2]

Although reductive cyclization proceeded rapidly and cleanly, a significant drawback of this method remained the somewhat tedious extraction of the indole from the aqueous reduction mixture, which contained titanium dioxide as a fine suspension. The tendency of this mixture to form emulsions decreased extraction efficiency and required the use of large solvent volumes for good product recovery.

A recent literature procedure[3] for the preparation of 4-(benzyloxy)indole uses Raney nickel and hydrazine hydrate to effect the reductive cyclization in high yield. We were curious to see if nickel boride (P-1 nickel) would also effect the reduction, as this catalyst is reported to be at least as active as Raney nickel in the hydrogenation of alkenes.[4] Obvious advantages over Raney nickel include its ease of preparation and nonpyrophoric nature.

Indeed, when an ethanolic solution of **1** in the presence of nickel boride was brought to reflux and several equivalents of hydrazine hydrate were added, gas was vigorously evolved and a rapid reductive cyclization occurred. After filtration, solvent removal, and flash chromatography,[5] 4-(benzyloxy)indole was obtained in 90% yield. In combination with the TPM condensation, this procedure may now be used easily to convert 2-(benzyloxy)-6-nitrotoluene to 4-(benzyloxy)indole in better than 80% overall yield with the use of inexpensive reagents and nonpyrophoric catalysts.



In a further investigation of the general utility of these reagents, we have discovered that similar reaction conditions also effect the reduction of aliphatic nitro compounds. Several substituted 1-(indol-3-yl)-2-nitroalkanes **4a–c** were reduced to the corresponding α-alkyltryptamines **5a–c** as illustrative examples. Indolylnitroalkanes were prepared by the condensation of substituted indoles **3a–c** with the appropriate nitroolefin, an extension of the method of Ranganathan.[6] It appears that a variety of substituted α-alkyltryptamines may be readily prepared by this two-step method.

Finally, it is interesting to note that while no use of nickel boride/hydrazine as a reduction system has been

(1) Leimbruber, W.; Batcho, A. D. Third International Congress of Heterocyclic Chemistry, 1971, Sendai, Japan.
(2) Lloyd, D. H.; Nichols, D. E. *Tetrahedron Lett.* **1983**, *24*, 4561.
(3) Leimgruber, W.; Batcho, A. D. *Org. Synth.* **1984**, *63*, 214.
(4) Brown, C. A. *J. Org. Chem.* **1970**, *35*, 1900.
(5) Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923.
(6) Ranganathan, D.; Rao, C. B.; Ranganathan, S.; Mehrota, A. K.; Iyengar, R. *J. Org. Chem.* **1980**, *45*, 1185.

0022-3263/86/1951-4294$01.50/0

reported in the literature, several references to the use of nickel boride coated carbon electrodes in hydrazine fuel cells do exist, indicating that an interaction between the catalyst and hydrazine has been known for some time.

Experimental Section

Melting points were determined in open glass capillaries using a Mel-Temp apparatus and are uncorrected. Proton NMR spectra were recorded on a Varian FT-80 spectrometer and chemical shifts are reported in parts per million relative to Me_4Si as the internal standard in deuteriochloroform ($CDCl_3$). The multiplicities are noted as: s = singlet, d = doublet, t = triplet, q = quartet, p = pentet, sx = sextet, m = multiplet, b = broad. Mass spectra were recorded on a Finnegan 2000 spectrometer and exact masses were determined on a Kratos MS50 mass spectrometer. Thin layer chromatography (TLC) was performed on 0.25-mm silica gel (SIL G/UV254) precoated plastic plates with visualization using UV light and (for indoles) Ehrlich's reagent (*p*-(dimethylamino)-benzaldehyde in ethanol with concentrated HCl).

Nickel Boride. The catalyst was prepared just prior to use by the dropwise addition of 2-molar equiv of sodium borohydride (1.0 M solution in 0.1 M aqueous sodium hydroxide) to a stirred 0.1 M solution of nickel(II) acetate tetrahydrate in a large beaker. Whereas previous procedures[4,7] stress the use of inert or hydrogen atmospheres during the catalyst preparation, this did not appear to be necessary when hydrazine hydrate was used as the hydrogen source. After gas evolution had completely ceased the aqueous solution was decanted, the black granular nickel boride was resuspended in distilled water, then again decanted. After several quick washings with water, the catalyst was washed twice with ethanol and transferred to a round-bottomed flask for use in the reduction.

2-(Benzyloxy)-6-nitro-2′-piperidinostyrene (1). Tripiperidinomethane (9.20 g, 34.7 mmol) and 2-(benzyloxy)-6-nitrotoluene (5.62 g, 23.1 mmol) were fused at 110 °C and stirred under an aspirator vacuum for 6 h, at which time reaction was complete as indicated by TLC (silica gel/dichloromethane). The reaction mixture was cooled, and 100 mL of absolute methanol was added. The product crystallized as bright red plates. Recovery by suction filtration, washing with a small amount of cold methanol, and drying at 2 mmHg afforded 7.31 g (93%) of 2-(benzyloxy)-6-nitro-2′-piperidinostyrene: 94–6 °C; NMR ($CDCl_3$) δ 7.40 (s, 5, Ph), 7.36–6.88 (m, 4, Ar and -CH=), 5.41 (d, 1, C=CH-), 5.10 (s, 2, OCH_2), 2.99 (bs, 4, N-CH_2), 1.54 (bs, 6, -CH_2-). Anal. Calcd: C, 71.0; H, 6.51; N, 8.28. Found: C, 70.80; H, 6.76; N, 8.10.

4-(Benzyloxy)indole (2). The 2-(benzyloxy)-6-nitro-2′-piperidinostyrene (1) (5.00 g, 14.8 mmol) was added to a stirred suspension of nickel boride (prepared from 15 mmol of nickel acetate) in 125 mL of absolute ethanol and the reaction mixture was heated to reflux. Hydrazine hydrate (1.5 g, 30 mmol) in 25 mL of absolute ethanol was added dropwise over 15 min, during which time vigorous evolution of gas occurred. TLC analysis of the mixture indicated reaction completeness. After cooling, the mixture was filtered through a pad of Celite and the filtrate was concentrated in vacuo. The resulting dark red residue was purified by flash chromatography (silica gel 1:1 toluene/cyclohexane) to afford 2.98 g (90%) of 4-(benzyloxy)indole as a white solid: 64–65 °C (lit.[3] 60–2 °C).

Preparation of 2-Nitropropene and 2-Nitro-1-butene. (prepared by the method of Ranganathan).[6] In a round-bottomed flask equipped with a Vigreux column and distilling head were placed 2-nitro-1-propanol (or 2-nitro-1-butanol) and 2.0 molar equiv of phthalic anhydride. The reactants were heated (oil bath) until a homogeneous solution was formed and the nitroolefin was distilled over at reduced pressure. A small amount of water which codistilled was removed with a disposable pipet, and the material was stored for future use as a benzene solution (1.0 g/10 mL) over anhydrous calcium chloride at 0 °C.

2-Nitropropene: pale-green liquid (bp 41 °C/76 mmHg); 94% yield; NMR ($CDCl_3$) δ 6.50 (s, 1, =CH), 5.80 (bs, 1, CH), 2.30 (s, 3, CH_3).

2-Nitro-1-butene: light-yellow liquid (bp 108 °C/61 mmHg); 79% yield, NMR ($CDCl_3$) δ 6.43 (s, 1, =CH), 5.56 (bs, 1, =CH), 2.59 (q, 2, CH_2), 1.17 (t, 3, CH_3).

Preparation of Indolylnitroalkanes 4a–c. To a stirred 0.5 M benzene solution of the appropriate indole was added 2 equiv of 2-nitropropene (or 2-nitro-1-butene) as a 10% benzene solution. The reaction mixture was heated at reflux under a nitrogen atmosphere until TLC analysis (dichloromethane/silica gel) indicated that all starting material was consumed. The dark reaction mixture was cooled to room temperature and quickly passed through a short silica gel column which was washed with 1:1 toluene/hexane until product recovery was complete. Solvent removal under reduced pressure afforded material which was sufficiently pure (by TLC) to be carried on to the next step without further purification.

1-(Indol-3-yl)-2-nitropropane (4a): isolated as an amber oil (81% yield); NMR ($CDCl_3$) δ 8.13 (bs, 1, NH), 6.80–7.80 (m, 5, Ar), 4.90 (sx, 1, CH), 3.28 (m, 2, CH_2), 1.50 (d, 3, CH_3); MS(EI), *m/z* (relative intensity) 204 (31), 158 (41), 157 (48), 130 (100).

1-[4-(Benzyloxy)indol-3-yl]-2-nitropropane (4b) (59% yield): obtained as an amber solid; mp 93–95 °C; NMR ($CDCl_3$) δ 7.95 (bs, 1, NH), 7.41 (bs, 5, PhH), 6.53–7.38 (m, 4, ArH), 5.13 (s, 2, OCH_2), 4.88 (sx, 1, CH), 3.22–3.32 (m, 2, CH_2), 1.22 (d, 3, CH_3); MS(EI), *m/z* (relative intensity) 310 (17), 173 (37), 172 (49), 91 (100); exact mass found 310.1323, calcd 310.1317.

1-(5-Methoxyindol-3-yl)-2-nitrobutane (4c) (69% yield): obtained as an amber oil; NMR ($CDCl_3$) δ 8.02 (bs, 1, NH), 6.78–7.27 (m, 4, ArH), 4.60–4.7 (m, 1, CH), 3.86 (s, 3, OCH_3), 3.05–3.55 (m, 2, $ArCH_2$), 1.77–2.09 (m, 2, CH_2), 0.97 (t, 3, CH_3); exact mass (EI), found 248.1167, calcd 248.1161.

Preparation of α-Alkyltryptamines 5a–c. To a stirred suspension of nickel boride in isopropyl alcohol prepared from 5.0 molar equiv of nickel acetate was added the indolylnitroalkane (**4a–c**) to form a 0.1 M solution. This was heated to reflux and a solution of 10.0 equiv of hydrazine hydrate in isopropyl alcohol was added dropwise at such a rate that the evolution of gas did not cause excessive foaming. After gas evolution was complete, reflux was continued for an additional 30 min, at which time TLC analysis indicated that the reaction was complete. The mixture was cooled to room temperature and filtered through a pad of Celite, and the filtrate was concentrated under reduced pressure. The residue was dissolved in dichloromethane and extracted with several portions of 10% acetic acid. The combined aqueous extracts were basified with ammonium hydroxide and the product was extracted into several portions of dichloromethane. The combined extracts were dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The α-alkyltryptamines (**5a–c**) were then recrystallized from diethyl ether.

1-(Indol-3-yl)-2-aminopropane (5a): obtained in 69% yield; mp 101–102 °C; NMR ($CDCl_3$) δ 8.13 (bs, 1, NH), 6.99–7.67 (m, 5, ArH), 2.34–3.43 (m, 3, $CHCH_2$), 1.46 (bs, 2, NH_2), 1.17 (d, 3, CH_3).

1-[4-(Benzyloxy)indol-3-yl]-2-aminopropane (5b): obtained in 71% yield; mp 151–153 °C; NMR ($CDCl_3$) δ 8.42 (bs, 1, NH), 6.50–7.52 (m, 9, ArH), 5.12 (s, 2, O-CH_2Ph), 2.52–3.26 (m, 3, $CHCH_2$), 1.20 (bs, 2, NH_2), 0.93 (d, 3, CH_3. Anal. Calcd: C, 77.11; H, 7.19; N, 9.99. Found: C, 76.64; H, 7.22; N, 9.83.

1-(5-Methoxyindol-3-yl)-2-aminobutane (5c): obtained in 75% yield; mp 110–112 °C; NMR ($CDCl_3$) δ 8.10 (bs, 1, NH), 6.77–7.30 (m, 4 ArH), 3.86 (s, 3, OCH_3), 2.41–3.49 (m, 3, $ArCH_2CH$), 1.20–1.56 (m, 2, CH_2), 1.48 (bs, 2, NH_2), 1.00 (t, 3, CH_3); exact mass (EI), found 218.1419, calcd 218.1419. Anal. Calcd: C, 71.53; H, 8.31; N, 12.83. Found: C, 71.64, H, 8.52; N, 12.75.

Acknowledgment. Support for this work was provided by PHS Grant DA-02189 from the National Institute on Drug Abuse.

Registry No. 1, 104324-89-2; 2, 20289-26-3; 3a, 120-72-9; 3c, 1006-94-6; 4a, 4771-72-6; 4b, 2873-49-6; 4c, 92108-71-9; 5a, 299-26-3; 5b, 2854-11-7; 5c, 4765-10-0; 2-(benzyloxy)-6-nitrotoluene, 20876-37-3; tripiperidinomethane, 22630-08-6; nickel boride, 12619-90-8; hydrazine hydrate, 7803-57-8; 2-nitropropene, 4749-28-4; 2-nitro-1-butene, 2783-12-2; 2-nitro-1-propanol, 2902-96-7; 2-nitro-1-butanol, 609-31-4.

(7) Schreifels, J. A.; Maybury, P. C.; Swartz, W. E., Jr. *J. Org. Chem.* **1981**, *46*, 1263.