Silica Gel Assisted Reductive Cyclization of 2-Nitro-β-piperidinostyrenes, Derived from 2-Nitrotoluenes, to Indoles

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An efficient modification of the Leimgruber-Batcho method of indole synthesis has been devised that facilitates the synthesis of a variety of 2,3-unsubstituted indoles containing halogen, methoxy and benzyloxy groups, from 2-nitrotoluenes, in high yields. The modified method involves the condensation of 2-nitrotoluenes with tripiperidinomethane followed by the reductive cyclization of the intermediate 2-nitro-β-piperidinostyrenes with iron and acetic acid in refluxing toluene in the presence of silica gel (column chromatography grade, 60-200 mesh).

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One of the most important methods for the preparation of many structurally diverse 2,3-unsubstituted indoles, is the Leimgruber-Batcho synthesis which involves aminovinylation of 2-nitrotoluenes followed by reductive cyclization of the resulting *trans*-β-dialkylamino-2-nitrostyrenes [1]. Variations of this method include the use of different aminomethylenating equivalents, *e.g.*, *N*,*N*-dimethylformamide dimethyl acetal (DMF-DMA) [1a-c], tripiperidinomethane (TPM) [2] and Gold's reagent [3]. A variety of different reducing agents, *e.g.*, palladium on charcoal-hydrogen [1a], Raney nickel-hydrogen [1a], Raney nickel-hydrazine [1c,4], nickel boride-hydrazine [5], iron-acetic acid [1b,6,7], tin(II) chloride-hydrochloric acid [7] and titanium(III) chloride [8], have been employed to effect reductive cyclization. One of the major advantages of this method is that it uses easily accessible 2-nitrotoluenes as starting materials.

We became interested in the Leimgruber-Batcho indole synthesis in connection with our syntheses of halogen substituted analogues of pharmacologically important neurotoxins 5,6- and 5,7-dihydroxytryptamines [9]. For these syntheses we needed access to the corresponding halogen substituted bis(benzyloxy)indoles unsubstituted in positions 2 and 3. The presence of both halogen and benzyloxy substituents in our target indoles precluded the use of catalytic methods for the reductive cyclization step. Application of either titanium(III) chloride-ammonium acetate or Raney nickel-hydrazine as the reducing agent, in conjunction with TPM for the condensation step, gave very low yields of indoles, *e.g.*, 5,6-bis(benzyloxy)-7-fluoroindole could be synthesized in 19 or 23% yield, respectively, using these reducing agents. We next considered the application of iron-acetic acid as the reducing agent even though very few examples exist on its application and the reported yields with this reagent are generally low [1b,6].

We felt that poor yields with iron-acetic acid as the reducing agent could be due to intermolecular reactions [10], between the starting β-dialkylamino-2-nitrostyrene and various reactive intermediates derived from it, leading to dimeric and/or polymeric by-products [11]. Our recent observations on the efficacy of silica gel as a supporting reagent for the reduction of β-nitrostyrenes [12a] and 2,β-dinitrostyrenes [12b] suggested that it may be possible to suppress these intermolecular reactions by conducting the reduction step in a suitable nonpolar solvent in the presence of silica gel.

Indeed we found that a variety of indoles can be produced in high yields when a mixture of the 2-nitro-β-piperidinostyrenes **2**, formed *in situ*, iron and acetic acid is refluxed in toluene in the presence of silica gel (column chromatography grade, 60-200 mesh). The results are summarized in Table 1. The optimum reaction time for the condensation step was dependent on the structure of the nitrotoluene **1** and was determined by monitoring the progress of the reaction by tlc and pmr. In all cases, the reductive cyclization was complete in less than 1 hour. Isolation of the indoles in each case was vastly simpler compared to the titanium(III) chloride method. The effectiveness of silica gel together with the nonpolar solvent, toluene, is best demonstrated by the comparison of yields obtained for entry 1 by the present method (82%) and the method [1b] employing iron-acetic acid-ethanol (17%).

With entry 7, significant amounts of more polar by-products were detected by tlc in both stages of the process. Not surprisingly, this indole was isolated in only 62% yield. However, it has not been established whether the by-products at the reductive cyclization stage arose from the by-products formed at the condensation stage.

Application of this method allowed the syntheses of several of our target indoles including, 5,6-bis(benzyloxy)-4-fluoro-, 5,6-bis(benzyloxy)-7-fluoro-, and 4,7-difluoro-5,6-diphenylmethylenedioxyindoles in 61, 53 and 53% overall yields, respectively, from the corresponding nitrotoluenes. The overall yield, in each case, was limited by the formation of unidentified side products during the condensation of nitrotoluenes with TPM. Complications at the conden-

Table 1

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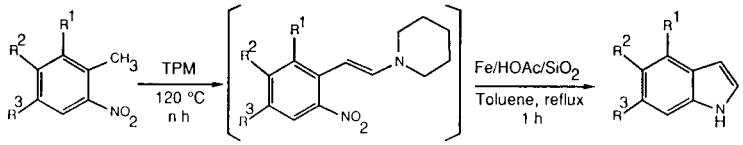

1 2 3

Entry	R^1	R^2	R^3	n (hours)	Yields (%) of Indoles [a]	mp, °C this study	mp, °C lit	Ref
1	H	H	H	5.5	82	50-52	52-54	[1c]
2	F	H	H	3	87	25-28	28-29	[14]
3	H	H	Cl	3	90	88	86-87	[1c]
4	CH_3O	H	H	4	94	68-69	69.5	[4]
5	$PhCH_2O$	H	H	4	85	71-72	72-74	[1c]
6	H	CH_3O	H	4	81	55-57	56-58	[1c]
7	H	$PhCH_2O$	$PhCH_2O$	5	62	112-113	113	[1c]

[a] Yields of pure indoles based on the nitrotoluenes

sation step were also responsible for only a 7% yield of 5,7-bis(benzyloxy) indole from 3,5-bis(benzyloxy)-2-nitrotoluene. This nitrotoluene reacted very slowly with TPM and when the reaction was allowed to proceed to completion (150 hours), only trace amounts of the desired nitrostyrene could be detected by tlc. Attempts to improve yields by using TPM or DMF-DMA at different temperatures in the presence or absence of a base catalyst (*e.g.* triethylamine [13] or DBU) were not successful.

In summary, condensation of a variety of 2-nitrotoluenes with TPM followed by the reductive cyclization of the intermediate nitrostyrene with iron-acetic acid in toluene in the presence of silica gel generally give 2,3-unsubstituted indoles in high overall yields. The overall yield appears to be limited mostly by the efficiency of the condensation step.

EXPERIMENTAL

Melting points were taken on a Thomas-Hoover melting point apparatus and are uncorrected. The pmr spectra were recorded in chloroform-d as a solvent with tetramethylsilane as the reference on Varian T-60 and Varian FT-80A instruments. Iron powder (reduced, N.F. IX electrolytic) and silica gel (60-200 mesh) used for the reactions as well as column chromatography were purchased from Mallinckrodt. Thin-layer chromatography was performed on silica gel plates (GHLF, 250 μ) purchased from Analtech. Tripiperidinomethane (TPM) [15] and 2-benzyloxy- [16] and 3,4-bis(benzyloxy)-6-nitrotoluenes [17] were prepared by published methods. Other nitrotoluenes were obtained from commercial suppliers and used without further purification.

General Procedure for the Synthesis of Indole **3** from Nitrotoluene **1** *via* 2-Nitro-β-piperidinostyrene **2**.

A mixture of 2-nitrotoluene **1** (2 mmoles) and TPM (3 mmoles) was heated to 120° and stirred under a water aspirator vacuum until the reaction was complete as judged by tlc (see Table 1). The crude 2-nitro-β-piperidinostyrene **2** was dissolved in a solution of toluene-acetic acid (5:3, 6 ml) and added to an efficiently stirred mixture of iron (2 g) and silica gel (5 g) in toluene-acetic acid (5:3, 26 ml) at room temperature. The mixture was then refluxed under an argon atmosphere for 1 hour and then cooled to 25°, diluted with methylene chloride (50 ml), and filtered. The filter cake was washed thoroughly with methylene chloride. The combined filtrates were washed successively with sodium metabisulfite solution, 10% sodium carbonate solution (until aqueous layer was basic) and brine. After drying over anhydrous sodium sulfate the solvent was evaporated *in vacuo*. The residue was chromatographed on a column of silica gel using methylene chloride-hexane as eluent to give indole **3**. The yields and melting points of the indoles are reported in Table 1. Satisfactory pmr spectral data were obtained for all of these indoles.

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REFERENCES AND NOTES

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[1a] W. Leimgruber and A. D. Batcho, Abstracts of Papers, Third International Congress of Heterocyclic Chemistry, Tohoku University, Sendai, Japan, Aug. 1971; [b] A. D. Batcho and W. Leimgruber, U. S. Patent 3,732,245 (1973); U. S. Patent 3,976,639 (1976); *Chem. Abstr.*, **86**, 29624t (1977); [c] A. D. Batcho and W. Leimgruber, *Org. Synth.*, **63**, 214 (1985); [d] R. D. Clark and D. B. Repke, *Heterocycles*, **22**, 195 (1984).

[2] D. H. Lloyd and D. E. Nichols, *Tetrahedron Letters*, **24**, 4561 (1983).

[3] J. T. Gupton, M. J. Lizzi, and D. Polk, *Synth. Commun.* **12**, 939 (1982).

[4] D. B. Repke and W. J. Ferguson, *J. Heterocyclic Chem.*, **19**, 845 (1982).

[5] D. H. Lloyd and D. E. Nichols, *J. Org. Chem.*, **51**, 4294 (1986).

[6] R. A. Glennon, E. Schubert, J. M. Jacyno and J. A. Rosencrans, *J. Med. Chem.*, **23**, 1222 (1980).)

[7] G. S. Ponticello and J. J. Baldwin, *J. Org. Chem.*, **44**, 4003 (1979).

[8] M. Somei, Y. Karasawa, T. Shoda and C. Kaneko, *Chem. Pharm. Bull.*, **29**, 249 (1981).

[9a] "Serotonin Neurotoxins", J. H. Jacoby and L. D. Lytle, eds, *Ann. N. Y. Acad. Sci.*, **305**, pp 1-702 (1978); [b] A. K. Sinhababu, A. K. Ghosh and R. T. Borchardt, *J. Med. Chem.*, **28**, 1273 (1985); [c] A. K. Sinhababu and R. T. Borchardt, *J. Am. Chem. Soc.*, **107**, 7618 (1985).

[10] J. Harley-Mason, *J. Chem. Soc.*, 200 (1953).

[11] The same reasoning may apply to other reducing agents as well, *cf.* L. I. Kruse, *J. Heterocyclic Chem.*, **16**, 1119 (1981).

[12a] A. K. Sinhababu and R. T. Borchardt, *Tetrahedron Letters*, **24**, 227 (1983); [b] A. K. Sinhababu and R. T. Borchardt, *J. Org. Chem.*, **48**, 3347 (1983).

[13] T. Tsuda, K. Yoshimoto and T. Nishikawa, *Chem. Pharm. Bull.*, **29**, 3593 (1981).

[14] T. Sugasawa, M. Adachi, K. Sasakura and A. Kitagawa, *J. Org. Chem.*, **44**, 578 (1979).

[15] R. A. Swaringen, Jr., J. F. Eaddy and T. R. Henderson, *J. Org. Chem.*, **45**, 3986 (1980).

[16] A. Stoll, *Helv. Chim. Acta*, **38**, 1452 (1955).

[17] H. G. Schlossberger and H. Kuch, *Chem. Ber.*, **93**, 1318 (1960).