HETEROCYCLES, Vol. 29, No. 3, 1989

A CONVENIENT REDUCTIVE CYCLISATION OF 2-NITRO-β-NITROSTYRENES TO INDOLES

Sundaramoorthi Rajeswari, Kevin J. Drost, and Michael P. Cava*

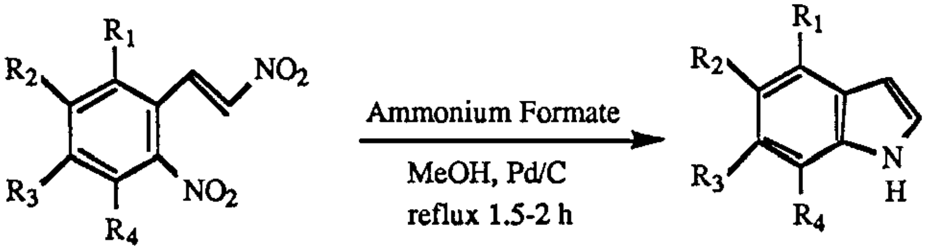
Department of Chemistry, The University of Alabama,
Box 870336, Tuscaloosa, AL 35487-0336, U.S.A.

Abstract - A simple synthesis of a variety of 2,3-unsubstituted indoles containing alkoxy and acetoxy groups has been developed. This method involves the reductive cyclisation of 2,β-dinitrostyrenes with ammonium formate in the presence of a catalytic amount of Pd/C in refluxing methanol, and affords indoles in good to excellent yields.

There is ongoing interest in the development of new and improved methods for the synthesis of the indole nucleus due to the biochemical and pharmacological importance of many of its derivatives.[1] One convenient method is the reductive cyclisation of 2,β-dinitrostyrenes using iron/acetic acid or catalytic hydrogenation.[2] (The 2,β-dinitrostyrenes are easily obtained in high yields from readily available o-nitrobenzaldehydes.) These reductive cyclisations, however, are neither clean nor high yielding. Conventional catalytic hydrogenation has resulted in poor yields and has only sparsely been used.[3,4] The earliest method developed and the one most widely used is iron/acetic acid reduction, but the procedures have given poor yields (15 - 55%)[2] and involved cumbersome workups. Recently, an improved iron/acetic acid reduction protocol using silica gel[5] has been reported, but this does not improve the yields greatly, and only moderately simplifies the workup. For this reason, we have proceeded to develop a better cyclisation technique, as exemplified for the conversion of 2,β-dinitrostyrenes (**1** - **8**) to indoles (**9** - **16**). The β-dinitrostyrenes were obtained by the facile condensation of substituted o-nitrobenzaldehydes with nitromethane in refluxing ammonium acetate/methanol.[6] We found that a variety of indoles (9 - 16) were produced in high yields (58-82%) when 2,β-dinitrostyrenes were reacted with ammonium formate and formic acid in refluxing methanol in the presence of Pd/C (5% by weight). Ammonium formate - Pd/C is reported as being a very versatile, selective and rapid method for catalyic hydrogenolysis.[7] In our reaction the products were easily purified and isolated by simple chromatography through silica gel. The results are summarized in Table I. In the case of the benzyloxy substituted nitrostyrene (7), the expected debenzylation[8] occurs and thus the product was acetylated before isolation.

Table 1

Ammonium Formate Reductive Cyclisation of 2,β-Dinitrostyrenes to Indoles



1 - 8 **9 - 16**

Entry	R_1	R_2	R_3	R_4	% yield[a]	% yield (lit.)	Ref.
1.	H	H	H	H	60	- - - -	6
2.	OCH_3	OCH_3	H	H	58	50[b]	9
3.	OCH_3	H	H	OCH_3	86	26[b]	8
4.	H	OCH_3	OCH_3	H	60	50[c]	4
5.	H	H	OCH_3	OCH_3	73	52[b], 23[c]	10, 3

Table 1 (Cont.)

Entry	R_1	R_2	R_3	R_4	% yield[a]	% yield (lit.)	Ref.
6.	H	H	OH	OCH_3	73	44[b]	11
7.	H	H	OC_6H_5[d]	OCH_3	74	15[b]	8
8.	H	-- O CH_2 O --		H	82	33[b]	12

---

[a] Ammonium formate - Pd/C procedure.

[b] Iron/acetic acid procedure.

[c] Catalytic hydrogenation procedure.

[d] Isolated as the acetate due to debenzylation during the reductive cyclization.

GENERAL PROCEDURE

To 2,β-dinitrostyrene (1mmol) and ammonium formate (10 mmol) in MeOH (10 ml) was added Pd/C (10%, 5% by wt.). The mixture was refluxed under N_2. After 1 h, formic acid (0.44 ml) was added and the mixture was refluxed until done as indicated by tlc (1/2 to 1 h). The mixture was filtered through celite, concentrated, and flashed through a short column of silica gel (CH_2Cl_2) to yield indoles **9 - 16**.

ACKNOWLEDGEMENT

We gratefully acknowledge the financial support of the National Institute of Health (Grant #CA 41995).

REFERENCES AND NOTES

1. W. T. Houlihan, "Indoles," Ed., Wiley Interscience: New York, Part I, 1972; b) ibid., Part 2, 1872; c) ibid., Part 3, 1979; d) G. A. Cordell, "Introduction to Alkaloids", Wiley Interscience: New York, 1981, Chapter 9; e) Manske, R. H. F., *The Alkaloids, Chemistry and Physiology*, Ed., Academic Press: New York, 1981, vol. 20 and other earlier volumes; f) N. Neuss, "Chemistry

of the Alkaloids," S. W. Pelletier, Ed., Var Noshand-Reinhold: New York, 1970, Chapter 9; g) A. Stoll and A. Hoffman, Ibid., Chapter 10; h) A. P. Kozikowski, Heterocycles, 1981, 16, 267; i) H. Achenbach, B. Raffelsberger, and I. Addalmensah, Liebigs Ann. Chem., 1982, 830.

2. R. T. Sundberg, "The Chemistry of Indoles", Academic Press, New York, 1970, Chapter 3; b) R. K. Brown, in ref 1a, Chapter 2; c) T. F. Spande, in ref. 1c Chapter 1; d) J. P. Kutney, "Total Synthesis of Natural Products", J. Apsimon, Ed. Wiley Interscience: New York, 1977; Vol. 3, p. 274.
3. F. Benington, R. D. Morin, and L. C. Clark, Jr., J. Org. Chem., 1959, 24, 917.
4. C. F. Huebner, H. A. Troxell, and D. C. Schroeder, J. Am. Chem. Soc., 1953, 75, 5887.
5. M. Kawase, A. K. Sinhababu, and R. J. Borchardt, J. Heterocyclic Chem., 1987, 24, 1499.
6. W. T. Houlihan, "Indoles," Ed. Wiley Interscience: New York, Part 1, 1972, pp. 455-595, 682-4.
7. S. Ram and R. E. Ehrenkaufer, Synthesis, 1988, 91.
8. G. Rodighiero, G. Malesemi, and U. Fornasiero, Gazz. Chim. Ital., 1961, 91, 742.
9. H. Burton and J. A. Duffield, J. Chem. Soc., 1949, 79.
10. A. de Antoni, G. Allegrie, and C. Costa, Gazz. Chim. Ital., 1970, 100, 1056.
11. R. J. S. Beer, K. Clarke, H. F. Davenport, and A. Robertson, J. Chem. Soc., 1951, 2029.
12. F. Dallacker and D. Bernabei, Monatsh.Chem., 1967, 98, 785.

Received, 11th October, 1988