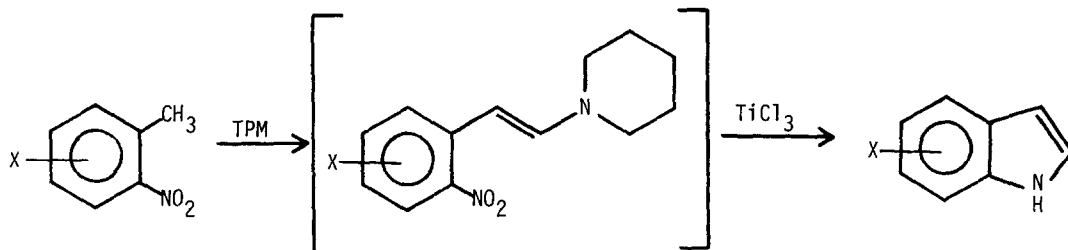


### A SIMPLE PROCEDURE FOR THE PREPARATION OF INDOLES

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Indoles are easily prepared in 60-70% yield from the corresponding o-nitrotoluenes by condensation with tripiperidinomethane, followed by reductive cyclization with aqueous titanous chloride.



Indoles are important starting materials for the synthesis of a variety of natural products and pharmacologically interesting compounds. While the patented procedure of Leimgruber and Batcho<sup>1</sup> represents a marked improvement over the Reissert method,<sup>2</sup> it was found to be ineffective for the preparation of 4-methoxy and 4-benzyloxyindole, which we required. The aminovinilation of 2-benzyloxy-6-nitrotoluene with dimethylformamide dimethylacetal (DMFDMA) is extremely sluggish.

We therefore investigated tripiperidinomethane (TPM) as a possible replacement for DMF acetals in a modified Leimgruber and Batcho scheme. TPM is easily prepared in large batches by the method of Swaringen et al.<sup>3</sup> When 2-benzyloxy-6-nitrotoluene is combined with 1.5 equivalents of TPM, heated to 110°, and stirred under a water aspirator vacuum (to remove piperidine) the condensation is complete within 4 hours. Reductive cyclization then affords the indole.

Among the many reagents available for the cyclization step, we have found  $TiCl_3$  to be the most convenient and rapid. Somei et al.<sup>4</sup> have also used  $TiCl_3$  in the preparation of 4-carbomethoxyindole. The crude  $\beta$ -piperidine-o-nitrostyrene is simply taken up into a minimum volume of acetone and added to a mixture of 6.2 equivalents of  $TiCl_3$ , as the commercially available 20% aqueous solution, and twice that volume of 4M  $NH_4OAc$  buffer, in a separatory funnel. The mixture is shaken for 5-10 minutes and the product is extracted into several portions of diethyl ether. After column chromatography (silica gel, benzene) 4-benzyloxyindole can be obtained in overall 62% yield from 2-benzyloxy-6-nitrotoluene.

We believe the TPM/ $TiCl_3$  method to be of general utility and have used it to prepare 4-methoxy, 5-methoxy, 6-methoxy, 4-benzyloxy, 5-benzyloxy, 4-chloro, and 4-cyano indole from the corresponding o-nitrotoluenes in 60-70% overall yield.

Other modifications of the Leimgruber and Batcho method have been recently reported which allow 4-alkoxyindoles to be prepared. Repke and Ferguson<sup>5</sup> have found that the addition of one equivalent of pyrrolidine to the DMFDMA condensation affords the desired  $\beta$ -aminostyrene. Kruse<sup>6</sup> has used another orthoamide, tris(N,N-dimethylamino)-methane, in the same context. Both procedures afford 4-benzyloxyindole in yields comparable to the TPM/ $TiCl_3$  method. While some investigators may find the commercial availability of DMFDMA and tris(N,N-dimethylamino)-methane attractive, we find the price of these reagents (particularly the latter) to be a disadvantage. We present tripiperidinomethane as an alternative reagent, easily prepared in large batches from piperidine and triethylorthoformate, both readily available and inexpensive.

#### ACKNOWLEDGMENT

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