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A General Synthesis of *N*-Hydroxyindoles

Audrey Wong,* Jeffrey T. Kuethe, and Ian W. Davies

Department of Process Research, Merck & Co., Inc., P.O. Box 2000, Rahway, New Jersey 07065

audrey_wong@merck.com

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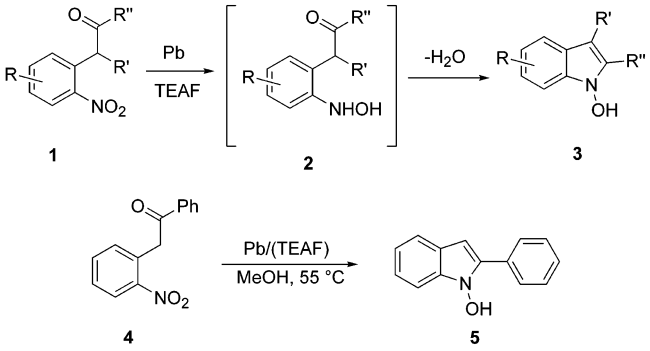
Abstract: A general method for the formation of *N*-hydroxyindoles is demonstrated through a lead-promoted intramolecular reductive cyclization of *o*-nitrobenzyl ketones and aldehydes under transfer hydrogenation conditions. The *N*-hydroxyindoles are isolated in high purity and excellent yield (>90%) in an operationally simple procedure. This new method is exemplified by a two-step synthesis of the naturally occurring 1-methoxyindole-3-carboxaldehyde, which is pivotal in many alkaloid total syntheses.

The synthesis of *N*-hydroxyindoles and their derivatives has received considerable attention in recent years.[1] The biological role of *N*-hydroxyindoles is still an area of significant investigation. A range of *N*-hydroxyindoles has been shown to have antimicrobial or fungicidal activity. In addition, biologically inactive indoles have been rendered biologically active when the *N*-hydroxyindole analogues were prepared.[1] Due to their ability to direct lithiations at the indole 2-position and also undergo both nucleophilic and electrophilic substitutions, *N*-hydroxy- and *N*-alkoxyindoles have served as useful precursors to highly functionalized indoles.[1] *N*-Hydroxyindoles are also convenient precursors to isatogens which have been shown to spin trap hydroxyl radicals[2] and exhibit a wide range of biological activities.[3] The ability to fully profile biological activity of *N*-hydroxyindoles has been somewhat limited by the currently available methods which suffer from low yields and competing side reactions. Although some of these limitations have been addressed by the Somei "*tungstate method*",[4] mild synthetic methods which would provide rapid assembly of the *N*-hydroxyindole ring from simple precursors would give access to an array of highly functionalized *N*-hydroxyindoles would be highly desirable. Reactions leading to increasing molecular complexity and methods which tolerate a wide range of functionality are important synthetic tools. It was envisioned that reductive cyclization of substituted *o*-nitrobenzyl ketones would be an attractive method for the construction of *N*-hydroxyindoles. In this paper, we demonstrate an efficient method for the synthesis of *N*-hydroxyindoles which is mild, high yielding and tolerates a wide range of functionality.

SCHEME 1



While the reduction of *o*-nitrobenzyl ketones or aldehydes has been reported to give *N*-hydroxyindoles in the presence of Zn/NH_4Cl,[5] $Pd/NaBH_4$,[6] or Pd/H_2,[7] these reactions are generally intolerable to many functional groups, low yielding, and substrate limited. Often, further reduction of the *N*-hydroxyindole to the corresponding indole is observed. The reduction of aromatic nitro compounds with triethylammonium formate (TEAF) in the presence of palladium on carbon leads to the formation of anilines.[8] Very recently, Gowda reported the reduction of nitro compounds to azo compounds using Pb/TEAF in methanol.[9] Under these reaction conditions, the initial reduction of the nitro group to a hydroxylamine was observed, and in certain cases the hydroxylamine was isolated in up to 30% yield. We envisioned that reductive cyclization of a suitably substituted *o*-nitrobenzyl ketone **1** mediated by Pb/TEAF might provide the appropriate chemoselectivity to provide *N*-hydroxyindoles **3** via the cyclization of intermediate **2** (Scheme 1).

To examine the Pb/TEAF-promoted reductive cyclization to *N*-hydroxyindoles, nitroketone **4**[10] was treated with Pb/TEAF in MeOH at 55 °C for 12 h and gave 2-phenyl-*N*-hydroxyindole **5** as the sole product in 94% isolated yield. There was no detectable amount of 2-phenylindole present in the crude reaction mixture (HPLC and ^1H NMR) as evidenced by comparison with an authentic sample. With this extremely gratifying result, we set out to examine the scope of the reaction. The method proved to be general and allowed access to a diverse array of highly functionalized *N*-hydroxyindoles

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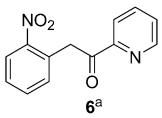
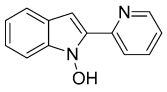
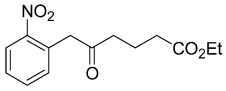
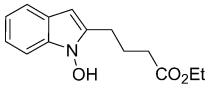
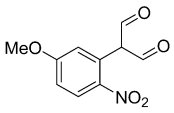
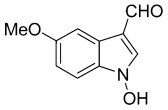
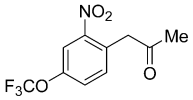
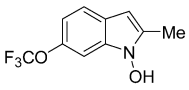
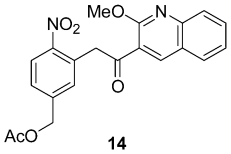
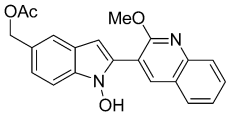
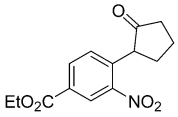
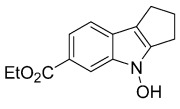
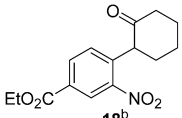
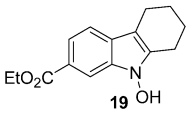
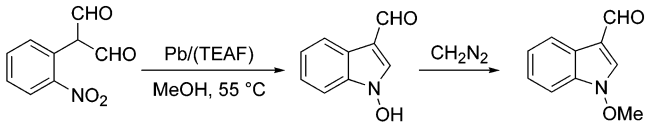
TABLE 1. Lead-Promoted Reductive Cyclization

Entry	Ketone	*N*-OH Indole	%Yield
1	 **6**[a]	 **7**[a]	92
2	 **8**[b]	 **9**	96
5	 **10**	 **11**	66
6	 **12**[c]	 **13**	95
7	 **14**	 **15**	71
8	 **16**[b]	 **17**	97
9	 **18**[b]	 **19**	94

[a] See ref 11. [b] See ref 12. [c] See ref 13.

in good to excellent yield (Table 1). Rapid two-step entry to substituted tricyclic systems of tetrahydrocyclopenta-[*b*]indoles (entry 8) and tetrahydrocarbazoles (entry 9) and the tolerance of a number of important functional groups have been demonstrated. In all cases, isolation of the product was achieved in a straightforward, simple fashion. The insolubles were removed by filtration, followed by concentration of the MeOH (or EtOH), and filtration through a small plug of silica gel which afforded the products as stable crystalline solids.

SCHEME 2



20 **21** **22**

Isolated from the Cruciferae family of plants,[1,14] 1-methoxyindole-3-carboxaldehyde **22** has been utilized as a building block for the synthesis of a number of other natural products.[15] The synthesis of **22** using the lead-promoted reductive cyclization required only two synthetic steps from commercially available 2-nitromalondialdehyde **20** and occurred in 89% overall yield (Scheme 2).

In summary, a general, high-yielding method of preparation of *N*-hydroxyindoles through the lead-promoted intramolecular reductive cyclization of *o*-nitrobenzyl ketones and aldehydes has been demonstrated. The reaction conditions are mild and tolerant of a wide range of functional groups. Increased access to *o*-nitrobenzylcarbonyl substrates through recent advances by Buchwald,[12] Rawal,[16] RajanBabu,[17] and others[18] and the present sequence should allow for the generation of previously inaccessible *N*-hydroxyindoles in a remarkably straightforward manner.

Supporting Information Available: Experimental procedures and compound characterization for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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