

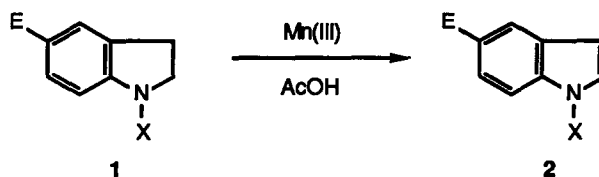
THE MANGANESE(III) ACETATE OXIDATION OF N-PROTECTED INDOLINES¹

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Summary: A variety of N-protected indolines can be oxidized to the corresponding indoles using manganese(III) acetate in glacial acetic acid.

The indoline-indole synthetic interconversion has been widely exploited for the selective functionalization of indoles.^{2,3} In this approach, electrophiles can be added to the normally unreactive carbocyclic ring while the indole is masked as an N-protected indoline.⁴ Oxidative regeneration of the indole nucleus at a later stage then allows for further elaboration of the molecule at carbons 3 or 2, the sites of normal reactivity. In this way, highly substituted indoles can be prepared from readily available precursors while avoiding *de novo* ring construction.



A wide array of oxidizing agents have been employed for this formal dehydrogenation; however, the effectiveness of any particular reagent is often limited by the nature and position of substituents attached to the indole ring. For instance, manganese dioxide⁵ fails to oxidize 2,3-dialkylindolines, and phenylseleninic anhydride⁶ produces 3-phenylselenoindoles from indolines lacking a 3-substituent. Reagents such as palladium on charcoal,⁷ and chloranil,⁸ although generally broader in scope, often require elevated temperatures or present problems in isolation. Furthermore, methods for the dehydrogenation of indolines requiring their *in situ* conversion to either azasulfonium salts or N-chloramines are necessarily limited to N-unsubstituted indolines.^{9,10}

In developing general strategies for the syntheses of indole natural products, we felt that early protection of the indolic nitrogen was of major importance, for the protecting group would serve to direct substitution as well as stabilize some of the required intermediates. Efficient oxidants for the dehydrogenation of representative N-protected indolines were therefore sought. Initial studies involving ruthenium tetroxide (biphasic conditions)¹¹ or ceric ammonium nitrate (CAN) with either **1a** or **1c** produced complex mixtures of products in each case.¹² The

reported formation of benzyl acetates from substituted toluenes using manganese(III) acetate¹³ indicated to us that a similar oxidation to form the indoline-3-acetate might occur with subsequent elimination to afford the fully aromatic indole.

Accordingly, a series of N-protected indolines was subjected to this oxidation. Interestingly, the only isolable products were the corresponding indoles. No evidence for the intermediacy of a benzylic acetate was observed; however, on the basis of the earlier finding, it is reasonable to invoke such an intermediate.

We find this reagent to be a mild and selective oxidant for the conversion of a variety of N-protected indolines into the corresponding indoles. As can be seen from Table 1, the indoline-indole conversion can be achieved in good to excellent yield. In general, the efficiency of this process is determined by the nature of the protecting group as well as the substituent on the benzene ring. Thus, while N-(N',N'-diethylcarbamyl)indoline (1a) can be oxidized in good yield (overnight) using only 1.2 equivalents of manganese(III) acetate (Aldrich) in acetic acid at room temperature, faster and more complete conversion is achieved at 70°C. All other examples investigated required higher temperatures and larger excesses of oxidant (2-4 equivs.) for complete reaction. In some cases, degradation of the substrate or product was responsible for the low yield. For instance, in the attempted oxidation of 1h, the indole 2h was isolated in 16% yield along with only 22% of recovered starting material.

Table 1. Oxidation of indolines (1) with Manganese(III) Acetate

Substrate (1)	X	E	mp(°C)	Reaction temp. (°C)	Yield, % ^{a,b} of 2	mp(°C)
1a	-CONEt ₂	-H	oil	70	82	oil
1b	-CONEt ₂	-Br	76-78	70	67	oil
1c	-PhSO ₂	-H	132-133	70	80	74-76 ¹⁴
1d	-PhSO ₂	-CH ₂ CH ₃ ¹⁵	70-71	90	61	oil
1e	-PhSO ₂	-CH ₂ Ph ¹⁵	79-81	90	55	oil
1f	-PhSO ₂	-Br	104-105	110	78	89-90
1g	-PhSO ₂	-CONEt ₂	100-102	110	67	oil
1h	-PhSO ₂	-CO ₂ Et	132-133	110	16	123-125
1i	-PhSO ₂	-COCH ₃	146-147	110	16	123-124
1j	-PhSO ₂	-COPh	142-144	110	43	122-124
1k	-PhSO ₂	-NO ₂	249-252	110	0 ^c	-
1l	-COCH ₃	-H	102-103	110	39	oil

^aYield after purification by flash chromatography.

^bAll compounds were fully characterized by IR, ¹H NMR, ¹³C NMR, and combustion analysis.

^cOnly starting material was recovered.

Further uses of this mild oxidant in the synthesis of highly substituted indole alkaloids, and the selective functionalization of the indole nucleus are currently under investigation.

Representative Procedure.

To a magnetically stirred suspension of manganese(III) acetate dihydrate (0.67 g, 2.5 mmol) in acetic acid (10 mL) at 70°C was added dropwise a solution of N-(N',N'-diethylcarbamy)indoline (**1a**) (0.50 g, 2.3 mmol) in acetic acid (5 mL). The mixture was stirred for 3 hours at 70°C and cooled to room temperature. The mixture was filtered, and the white precipitate (presumably Mn(II) acetate) was washed with 150 mL of CH₂Cl₂. The organic layer (filtrate plus CH₂Cl₂) was then washed with water, saturated aqueous NaHCO₃ and brine, dried (K₂CO₃) and evaporated in vacuo to a brown oil, which, after flash chromatography¹⁶ using CH₂Cl₂/hexanes, afforded pure N-(N',N'-diethylcarbamy)indole (**2a**) as an orange oil (0.44 g, 82%).

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4. NOTE: While it is not always necessary to employ N-protected indolines in order to introduce electrophiles to the benzene ring, the protected indolines in this study were prepared from freshly distilled indoline and either benzenesulfonyl chloride, diethylcarbamoyl chloride, or acetic anhydride in the presence of pyridine. The introduction of acyl substituents onto the 5-position of the protected indolines were conducted following the general procedure for the Friedel-Crafts acylation of N-protected indoles: Ketcha, D.M. and Gribble, G.W. *J. Org. Chem.*, **1985**, 50, 5451.
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