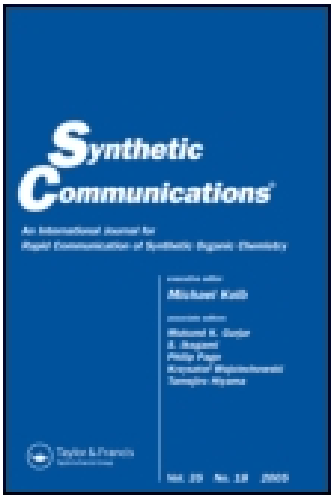

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Manganese(III) Acetate Oxidation of Alkyl Substituted 1-(Phenylsulfonyl)indoles

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MANGANESE(III) ACETATE OXIDATION OF ALKYL SUBSTITUTED 1-(PHENYLSULFONYL)INDOLES

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ABSTRACT: Methyl substituted 1-(phenylsulfonyl)indolines undergo tandem oxidation of the indoline ring and a C-2 methyl group. If there is no alkyl substituent at the C-2 position, nuclear acetoxylation can occur to afford oxindoles.

Recently, we reported that manganese(III) acetate is capable of effecting the oxidation of a variety of N-protected indolines to the corresponding indoles.[1] The choice of this oxidant was predicated on the well known ability of Mn(III) to effect acetoxylation of the benzylic carbons of substituted toluenes.[2-6] Thus, viewing indolines as alkyl substituted anilines, it was expected that acetoxylation of the benzylic C-3 position of the indoline ring would be followed by spontaneous elimination of acetic acid to afford the fully aromatic indole species.

Since this dehydrogenation is essentially an example of a benzylic acetoxylation, it was decided to expand the scope of our initial investigations and study the oxidation of 1-(phenylsulfonyl)indolines bearing alkyl substituents at the C-2 and/or C-3 positions. In this way, oxidation of the ring might then be followed by tandem oxidation of the nascent benzylic carbons of the alkyl side chains.

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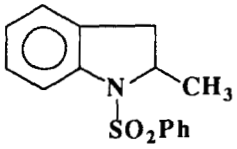
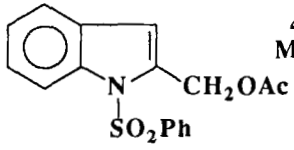
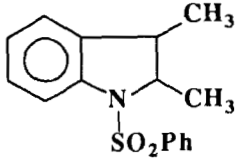
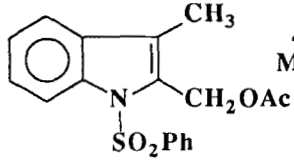
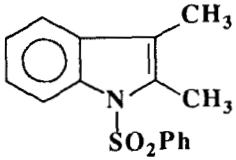
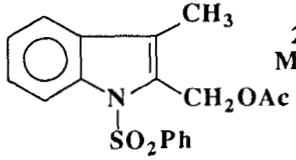
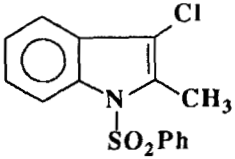
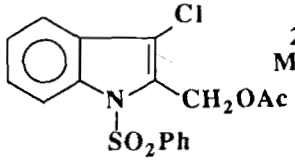
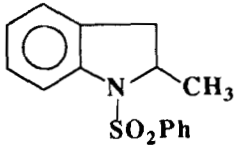
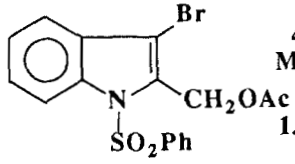
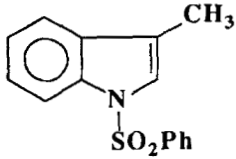
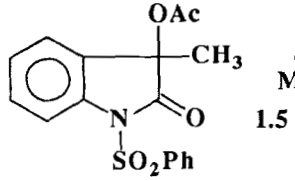
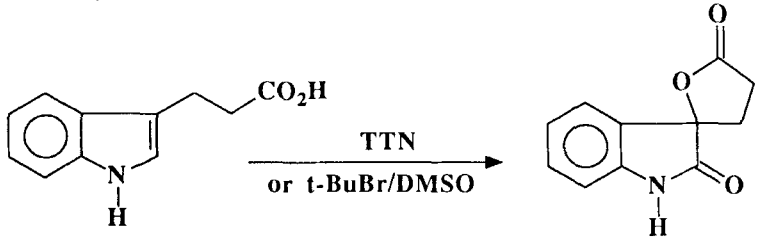
Due to the electron-rich nature of the heterocyclic ring of indoles, benzylic oxidation of an alkyl group at either the C-2 or C-3 position is possible. However, an earlier report[7] on a similar oxidation of 2,3-dimethylindole using lead(IV) acetate seemed to indicate that the C-2 methyl group would be more susceptible to acetoxylation. Indeed, this same regioselectivity was observed in the case of alkyl substituted 1-(phenylsulfonyl)indoles as seen in the Table. In these examples, 2-methyl- and 2,3-dimethyl-1-(phenylsulfonyl)indoline[8] (entries **a** and **b**) underwent sequential oxidation to the indole oxidation level followed by selective acetoxylation of the C-2 methyl groups using 4 equivalents of Mn(III). If the substrates were already at the indole oxidation level as in the case of 2,3-dimethyl- or 3-chloro-2-methyl-1-(phenylsulfonyl)indole[9] (entries **c** and **d**), 2 equivalents of Mn(III) were sufficient to effect acetoxylation of the C-2 methyl groups. In general, the yields of these acetoxylations ranged from 53-66% and compare with similar benzylic acetoxylations of substituted toluenes, especially as some of the reactions are "one-pot", two step sequences.

The acceleration of Mn(III) side chain oxidations by bromide ion has been reported,[6,10] and while the mechanism may differ from the non-catalyzed reaction, the same side chain acetates (or bromides) can be obtained in high yield. It was therefore of interest to examine the effect of bromide in the present situation. While in no instance was the process improved by the addition of KBr, interestingly in one case (entry **e**) an electrophilic bromine species (or radical) has apparently added to the C-3 position subsequent to the oxidation of the ring since a 3-bromo acetoxylated indole was obtained in 58% yield.[11]

In the case of 3-methyl-1-(phenylsulfonyl)indole[12] (entry **f**) which lacks a C-2 substituent, the product of Mn(III) oxidation in the presence of KBr was not the result of an expected acetoxylation of the C-3 methyl group, but instead was shown

Entry	Substrate	Product	Oxidant	mp (°C)	Yield
a			4 eq Mn(III)	81-3	61%
b			4 eq Mn(III)	123-4	66%
c			2 eq Mn(III)	123-4	58%
d			2 eq Mn(III)	117-19	53%
e			4 eq Mn(III) 1.5 eq KBr	103-5	58%
f			4 eq Mn(III) 1.5 eq KBr	147-50	54%

by X-ray crystallographic analysis[13] to be 3-acetoxy-3-methyl-1-(phenylsulfonyl)-oxindole. It is believed that this product is the result of an initial nuclear acetoxylation of the C-2 position followed by hydrolysis and isomerization to an oxindole which undergoes subsequent acetoxylation of the C-3 benzylic position. A similar oxidation of indole-3-propionic acid to an oxindole using thallium(III) nitrate (54%)[14] or t-BuBr/DMSO (80%)[15] wherein an intramolecular cyclization of the carboxylic acid function occurred to afford the spirocyclic lactone shown:



Considering the relatively high cost of $Mn(OAc)_3 \cdot 2H_2O$, attempts were made to use either a catalytic amount of Mn(III) or the less expensive $Mn(OAc)_2 \cdot 4H_2O$ along with a cooxidant. Since Dicosimo et al.[16] demonstrated that peracetic acid could function as a useful cooxidant for the Co(III) oxidation of benzene to phenol, a related oxidation of 2,3-dimethyl-1-(phenylsulfonyl)indoline was attempted using peracetic acid in the presence of a catalytic amount of Mn(III), however, only a 14% yield of the corresponding C-2 acetoxylated indole was obtained. Similarly, nonanoic acid has been described as a cooxidant and solvent[17] for Mn(III) oxidations (presumably via the peracid generated in-situ from air). However, this method again proved unsatisfactory for our case and while in principle, the use peracids as cooxidants for Mn(III) mediated oxidations appears promising, the recent finding that N-benzenesulfonylindoles react readily with peracids to afford 3-indolinones[11c] indicates that their utility with π-excessive heterocycles may be limited.

Another relatively simple method for generating Mn(III) from Mn(II) involves treating manganese(II) nitrate with acetic anhydride.[18] However, this method also proved ineffective for the oxidation of N-protected indolines.

In conclusion, it is demonstrated that tandem oxidations of alkyl substituted indolines can be effected to preferentially afford C-2 acetoxylated indoles in good yields. If, however, there is no substituent at the C-2 position, nuclear acetoxylation can take place at this site to afford oxindoles (2-indolinones). The extension of this methodology to the synthesis of natural products including the mitosene skeleton is currently under investigation.

EXPERIMENTAL

Melting points were determined in open capillaries with an Electrothermal melting point apparatus and are uncorrected. Elemental analyses were performed by Midwest Microlab, Indianapolis, IN. Infrared spectra were recorded on a Perkin-Elmer 1330 instrument or with a Nicolet 5DX Fourier transform (FT) instrument. NMR spectra were obtained on a Varian EM 360 or an IBM NR/100FT NMR. Chemical shifts are reported in parts per million downfield from tetramethylsilane as an internal reference. Low resolution mass spectra were determined with a Finnigan MAT INCOS 50 gas chromatograph-mass spectrometer. Sodium borohydride (pellets),*tert*-butylamine-borane complex (pellets), and manganese(III) acetate were purchased from Aldrich Chemical Co.

Preparation of *cis*-2,3-dimethyl-1-(phenylsulfonyl)indoline.

To a vigorously stirred suspension of 2,3-dimethylindoline (6.13 g, 42 mmol) in 10% NaOH (100 mL) was added benzenesulfonyl chloride (14.71 g, 10.63 mL, 83.3 mmol) and the mixture was stirred for 30 min at 25 °C. The aqueous layer was decanted from the gummy residue which was taken up in methanol, treated with charcoal, and recrystallized to afford *cis*-2,3-dimethyl-1-(phenylsulfonyl)-indoline, 10.99 g (91.2%, two crops): mp 110-112 °C (lit.[8] mp 113-114 °C).

Preparation of 3-methyl-1-(phenylsulfonyl)indole.

To a magnetically stirred mixture of *tert*-butyl ammonium hydrogen sulfate (1.30 g, 3.82 mmol) in 50% NaOH (200 mL) was added a solution of 3-methylindole (5.0 g, 38.2 mmol) in CH_2Cl_2 (150 mL). Benzenesulfonyl chloride (22 mL, 30.4 g, 4.5 eq) in 20 mL CH_2Cl_2 was added, and the solution stirred overnight. The mixture were filtered and the filtrate extracted with CH_2Cl_2 (2 x 50 mL). The combined organic layers were washed with water, brine, dried (K_2CO_3), and concentrated in vacuo. Chromatography on silica gel with CH_2Cl_2-hexane (70/30, v/v) provided 9.34 g (90%) of 3-methyl-1-(phenylsulfonyl)indole. Crystallization from methanol afforded the pure product: mp 117-120 °C (lit.[12] mp 120-122 °C) which was identical to a sample previously prepared in this laboratory.[11b]

Preparation of 3-methyl-2-acetoxymethyl-1-(phenylsulfonyl)indole. (General procedure for Mn(III)/AcOH oxidations)

A solution of 2,3-dimethyl-1-(phenylsulfonyl)indoline (6.19 g, 21.6 mmol) and manganese(III) acetate dihydrate (23.14 g, 86.3 mmol) in 150 mL of acetic acid was stirred at 120 °C overnight. Water (100 mL) was added and the mixture was extracted with CH_2Cl_2 (3 x 50 mL). The combined the organic layers were washed with saturated aqueous $NaHCO_3$, water, brine, dried over anhydrous $MgSO_4$ and evaporated in vacuo. The residue was purified by column chromatography (silica gel) with CH_2Cl_2 to give 4.88 g (65.9%) of the acetoxylated indole: mp 123-124 °C; IR (KBr) 3060, 2980, 1735, 1450, 1370, 1230, 1175, 1100, 965, 765, 755, 600 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.15-8.3 (9H, m), 5.5 (2H, s), 2.25 (3H, s), 2.0 (3H, s); mass spectrum, *m/z* 343 (M^+), 284, 161, 160, 159, 143, 142 (100), 115, 77. Anal. Calcd for $C_{18}H_{17}NO_4S$: C, 62.95; H, 4.99; N, 4.08; S, 9.34. Found: C, 62.98; H, 4.88; N, 4.00; S, 9.29.

Preparation of 2-acetoxymethyl-1-(phenylsulfonyl)indole.

Using the procedure described above with 2-methyl-1-(phenylsulfonyl)indoline afforded the product (61%): mp 81-83 °C; IR (KBr) 3060, 2940, 1740, 1595, 1450, 1370, 1225,1180, 1165, 1150, 930, 915, 825, 765, 735, 600, 570 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.1-8.2 (9H, m), 6.6 (1H, s), 5.4 (2H, s), 2.0 (3H, s); mass spectrum, *m/z* 329 (M^+), 146 (100), 145, 129, 118, 117, 102, 77, 51. Anal. Calcd for $C_{17}H_{15}NO_4S$: C, 62.00; H, 4.59; N, 4.25. Found: C, 62.16; H, 4.46; N, 4.24.

Preparation of 3-chloro-2-acetoxymethyl-1-(phenylsulfonyl)indole.

Using the procedure described above but with 2eq of Mn(III) and 3-chloro-2--methyl-1-(phenylsulfonyl)indole[9] gave the product (53%): mp 117-119 °C; IR (KBr) 3060, 3010, 2970, 2930, 1730, 1580, 1450, 1380, 1250, 1180, 1100, 1030, 1000, 980, 760,740, 570 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.15-8.25 (9H, m), 5.5-5.6 (2H, s), 1.9-2.05 (3H, s); mass spectrum, *m/z* 363 (M^+), 204, 180, 163, 128, 144, 117, 77 (100), 51. Anal. Calcd for $C_{17}H_{14}NO_4SCl$: C, 56.12; H, 3.88; N, 3.85. Found: C, 56.90; H, 3.89; N, 3.81.

Catalysis with KBr. Using the procedure described above but with 1.5 eq of KBr afforded the product in 41.4% yield: mp 115-116 °C. Anal. Calcd for $C_{17}H_{14}NO_4SCl$: C, 56.12; H, 3.88; N, 3.85. Found: C, 56.21; H, 3.88; N, 3.90.

Preparation of 3-bromo-2-acetoxymethyl-1-(phenylsulfonyl)indole.

Using the procedure described above but with 1.5 eq of KBr and 2-methyl-1 -(phenylsulfonyl)indoline gave the product (57.9%): mp 103-105 °C; IR (KBr) 3080, 2980, 1740, 1460, 1375, 1245, 1190, 1040, 1105, 750, 595, 580 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.2-8.3 (9H, m), 6.45-6.6 (2H, s), 1.95-2.1 (3H, s); mass spectrum, *m/z* 409, 407(M^+), 286, 223 (100), 207, 144, 128, 116, 77, 51. Anal.

Calcd for $C_{17}H_{14}NO_4SBr$: C, 50.00; H, 3.43; N, 3.43. Found: C, 49.64; H, 3.23; N, 3.47.

Preparation of 3-methyl-3-acetoxyl-1-(phenylsulfonyl)indol-2-one.[13]

Using the procedure described above but with 1.5eq of KBr and 3-methyl-1--(phenylsulfonyl)indole gave the product (53.5%): mp 150.5-151.5 °C; IR (KBr) 3080, 3000, 2700, 1785, 1765, 1620, 1480, 1470, 1375, 1245, 1180, 1100, 975, 765, 735, 695, 600 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.05-8.1 (9H, m), 1.9-2.0 (3H, s), 1.5-1.65 (3H, s); mass spectrum, *m/z* 345 (M^+), 303, 162 (100), 145, 117, 90, 77, 51. Anal. Calcd for $C_{17}H_{15}NO_5S$: C, 59.13; H, 4.35; N, 4.06. Found: C, 59.24; H, 4.18; N, 4.07.

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REFERENCES

1. Ketcha, D.M., Tetrahedron Lett., 1988, 29, 2151.
2. For a review on the acetoxylation of carbon with metal salts, see: Rawlinson, D.J. and Sosnovsky, G., Synthesis, 1973, 567.
3. Andrulis, P.J., Jr., Dewar, M.J.S., Dietz, R. and Hunt, R.L., J. Am. Chem. Soc., 1966, 88, 5473.
4. Eberson, L., J. Am. Chem. Soc., 1967, 89, 4669.
5. Heiba, E.I., Dessau, R.M., Koehl and W.J., Jr., J. Am. Chem. Soc., 1969, 91, 138.

6. Gilmore, J.R. and Mellor, J.M., J. Chem. Soc., Chem. Commun., 1970, 507.
7. Taylor, W. I., Abstr. 144th Meeting ACS, Los Angeles, 1963, p. 31 M.
8. Ketcha, D.M. and Lieurance, B.A., Tetrahedron Lett., 1989, 30, 6833. **Note**: This publication mistakenly assigns the major indoline product arising from the $NaCNBH_3$/TFA reduction of 2,3-dimethyl-1-(phenylsulfonyl)indole as the *trans*-isomer, thus perpetrating a common error existing in the literature of indoles. Therefore, it seems appropriate to reiterate the correct assignments as demonstrated in the Ph.D. dissertation of J.M. Muchowski, University of Ottawa, 1962, wherein the *cis*-isomer has mp 113-114°C, the *trans*-isomer has mp 101-103°C, and the 1:1 mixture of the two has mp 76-77°C.
9. (a) Dalton, L., Humphrey, G.L., Cooper, M.M. and Joule, J.A., J. Chem. Soc. Perkin Trans. I, 1983, 2417; (b) Bergman, J. and Pelcman, B. Tetrahedron, 1988, 44, 5215.
10. Van Der Ploeg, R.E., De Korte, R.W. and Kooyman, E.C., J. Catalysis, 1968, 10, 52.
11. For examples of the electrophilic addition of Br_2 to 1-(phenylsulfonyl)indole, see: (a) Gribble, G.W. and Barden, T.C., J. Org. Chem., 1985, 50, 5900; (b) Ketcha, D.M., Lieurance, B.A., Homan, D.F.J. and Gribble, G.W., J. Org. Chem., 1989, 54, 4350; (c) Conway, S.C. and Gribble, G.W., Heterocycles, 1990, 30, 627.
12. Wenkert, E., Moeller, P.D.R. and Piettre, S.R., J. Org. Chem., 1987, 52, 3404.
13. Grossie, D.A. and Ketcha, D.M., Acta Cryst., 1992, C48, 1718.
14. (a) Ohnuma, T., Kimura, Y. and Ban, Y., Tetrahedron. Lett., 1981, 22, 4969; (b) Ohnuma, T., Kasuya, H., Kimura, Y. and Ban, Y., Heterocycles 1982, 17, 377.

15. Labroo, R.B., Labroo, V.M., King, M.M. and Cohen, L.A., J. Org. Chem., 1991, 56, 3637.

16. DiCosimo, R. and Szabo, H-C., J. Org. Chem., 1986, 51, 1365.

17. Levy, L. B. J. Org. Chem., 1989, 54, 253.

18. (a) Chre'tein, A. and Varga, G., Bull. Soc. Chim. France, 1936, [5] 3, 2387.
(b) Lux, H.," Handbook of Preparative Inorganic Chemistry"; Brauer, G., Ed.; Academic Press: New York, 1965; pp 1470.

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