Manganese(III) acetate mediated oxidation of 1-alkyl-1H-indole and 9-methyl-9H-carbazole derivatives

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Abstract

Manganese(III) acetate mediated oxidation of 1-alkyl-1H-indole and 9-methyl-9H-carbazole was studied. 1-Methyl-1H-indole gives the 1-acetoxymethyl derivative with good yield. 1-Methyl-2-phenyl-1H-indole furnished the oxidation of the methyl group and C-3 of indole to obtain the corresponding acetox derivatives. 1-ethyl-2-phenyl derivative only furnished the C-3 acetoxylation product. 1,2-Dimethyl-1H-indole furnished oxidation on both of the methyl groups. The major products are 1-methyl-1H-indole-2-carbaldehyde and 1-methyl-2-diacetoxymethyl-1H-indole. Manganese(III) acetate oxidation of 9-methyl-9H-carbazole furnished (9H-carbazol-9-yl)methanol in good yield.

Keywords: Indole, carbazole, oxidation, manganese(III) acetate

Introduction

Metal-promoted radical reactions have found widespread use in organic synthesis, in which one of the well-known examples of this application is the manganese(III) acetate mediated reactions.\textsuperscript{1} The exciting development in this area is beginning to show its true potential, as evidenced from the application of this methodology in strategy-level bond formation during the synthesis of complex molecules. Manganese(III) acetate dihydrate (abbreviated hereinafter as Mn(OAc)\textsubscript{3}) mediated free radical reactions have emerged as important synthetic methods for a new bond formation and bond breaking.\textsuperscript{2}

Mn(OAc)\textsubscript{3} constitutes a mild one-electron oxidant. Direct inner-or outer-sphere one-electron oxidations with Mn(OAc)\textsubscript{3} in many cases proceed via the primary formation of an intermediate radical. The fate of this primary radical depends on the nature of the substrate and reaction
conditions. The Mn(OAc)$_3$ mediated selective oxidation of the common functional groups (C=C, C=O, C-O, COOH, etc.) is important in the synthesis of complex natural products$^{2a,3,4}$ but the oxidation of amine compounds is not yet well developed. As an example, the oxidation of N-substituted anilines is exemplified by Dewar,$^5$ and Rindone.$^6$ At room temperature, in acetic acid or chloroform-acetic acid mixtures, the main product from $N,N$-dimethylaniline is $N$-methylacetamide. In a comparative study with Pb(IV) acetate, Co(III) acetate, Tl(III) acetate, and Mn(OAc)$_3$ it was shown that the later oxidant gives cleaner reactions and the highest yields of amides.$^6$ The oxidation products of 1-methyl-$1H$-indole$^7$ and 9-methyl-$9H$-carbazole$^8$ derivatives are interesting intermediates for studying some biological processes, interesting industrial materials, and pharmaceutical compounds.$^7$ In our ongoing works we have published several papers concerning the Mn(OAc)$_3$-mediated direct oxidation and C-C bond formation reactions.$^{2a,3a}$ In this work we are describing Mn(OAc)$_3$ mediated oxidation of 1-methyl-$1H$-indole and 9-methyl-$9H$-carbazole derivatives.

Results and Discussion

According to the improved procedure for the Mn(OAc)$_3$ mediated oxidation reactions$^9$, commercially available 1-methyl-$1H$-indole is refluxed with Mn(OAc)$_3$ in benzene/AcOH (10:1) under Dean-Stark trap, and the reaction is monitored by TLC. After 6h no more changes to the reaction were observed. After the work up of two definable products, 1-acetoxymethyl-$1H$-indole (2) (56%) and (1$H$-indol-1-yl)methanol (3)$^{7a,b}$ (11% yield) were isolated together with the undefined mixture of the products. The 1-acetoxymethyl-$1H$-indole (2) is converted to 1-hydroxymethyl derivative 3 by using the common methods from the literature.$^{7b}$ Many attempts were made for increasing the yields but all without any success (Scheme 1).

![Scheme 1](image)

Under the above-mentioned conditions, indole itself gave no product and was mainly unchanged. Deactivation of the Mn(OAc)$_3$ by free amine (very fast disappearance of the brown color of the reaction) could be the reason for the recovery of the starting material.

The next oxidation reaction was carried out with the substituted derivatives of 1-methyl-$1H$-indole. The reaction of the commercially available 1-methyl-2-phenyl-$1H$-indole (4) with
Mn(OAc)$_3$ under the above-mentioned conditions was monitored by TLC. When nearly all of the starting material was consumed, three different products were formed. The products were identified as 1-methyl-2-phenyl-1$H$-indol-3-yl acetate 5 (23%); (2-phenyl-1$H$-indol-1-yl)methyl acetate 6 (18%) and 1-[(acetoxy)methyl]-2-phenyl-1$H$-indol-3-yl acetate 7 (45%) after the separation of the crude mixture by column chromatography (Scheme 2).

![Scheme 2](image)

**Scheme 2**

Monitoring the reaction by TLC and NMR showed that the first oxidation took place at C-3 to form 5, and then at N-$CH_3$ to form 6. Additional use of Mn(III) acetate along with a prolonged reaction time furnished 7 in 45% yields.

As shown in scheme 3, by using 1-ethyl-2-phenyl-1$H$-indole (8) instead of 4, the C-3 oxidized product 1-ethyl-2-phenyl-1$H$-indol-3yl acetate (9) was obtained in a 66% yield. Trace amount of N-$CH_2$ acetoxylation product is also obtained (from crude NMR).

![Scheme 3](image)

**Scheme 3**

Similar regioselectivity was found by the oxidation of methyl 1-methyl-1$H$-indole-2-carboxylate (10). Accordingly 10 furnished methyl 3-acetoxy-1-methyl-1$H$-indole-2-carboxylate (11) and methyl 3-acetoxy-1-(acetoxymethyl)-1$H$-indole-2-carboxylate (12) in 44% and 26% yields, respectively (Scheme 4). The products were separated by column chromatography and identified by NMR spectroscopy.
Next, we conducted the Mn(OAc)$_3$ oxidation study with the commercially available 1,2-dimethyl-1$H$-indole (13). After all of the starting material consumed (7h), four different products were formed. The products were separated by column chromatography and identified as (1-methyl-1$H$-indol-2-yl)methyl acetate (14)$^3$ (8%), {1-[(acetyloxy)methyl]-1$H$-indol-2-yl}methyl acetate (15) (10%), (acetyloxy)(1-methyl-1$H$-indol-2-yl)methyl acetate (16) (54%), and 1-methyl-1$H$-indole-2-carbaldehyde (17)$^7$k (19%). No C-3 oxidation product was observed (Scheme 5). According to the formation sequence of the compounds, first 14 and then 15 finally 17 formed. The formation of 16 from 14 worked faster than other derivatives. This was also proved by the Mn(OAc)$_3$ reaction of the isolated 14, which gives 16 as major and 17 as minor products.

The ability of Mn(OAc)$_3$ to oxidize the methyl group was examined by 9-methyl-9$H$-carbazole (18). As described by the indole case, 18 was refluxed with Mn(OAc)$_3$ in benzene/AcOH until no more conversion was observed (10h). In addition to several undefined products, (9$H$-carbazol-9-yl)methanol (19) was isolated in 67% yield (Scheme 6). 19 is an important compound by the metabolic study of 18$^8$, which is synthesized in the literature via the N-hydroxymethylation of carbazole with formalin over the basic alumina all under solvent-free conditions with microwave heating.$^8$d
In conclusion, we studied the manganese (III) acetate oxidation of indole derivatives and found that indole gives no product; 1-methyl-1H-indole selectively produces the oxidation of the methyl group in order to form 1-acetoxymethyl-1H-indole (2) in 56% yield. With 1-methyl-2-phenyl-1H-indole (4), 1-methyl-2-phenyl-1H-indol-3-yl acetate (5) (23%); (2-phenyl-1H-indol-1-yl)methyl acetate (6) (18%) and 1-[(acetoxy)methyl]-2-phenyl-1H-indol-3-yl acetate (7) (45%). The methyl group has the priority. In the case of the methyl 1-methyl-1H-indole-2-carboxylate (10) acetoxylation of methyl, the C-3 position was observed. 1,2-dimethyl-1H-indole (13) furnished the oxidation products in both methyl groups. The major products were (acetyloxy)(1-methyl-1H-indol-2-yl)methyl acetate (16) (54%) and 1-methyl-1H-indole-2-carbaldehyde (17) (19%). The Mn(OAc)₃ oxidation of 9-methyl-9H-carbazole (18) furnished (9H-carbazol-9-yl)methanol (19) in 67% yield.

**Experimental Section**

**General procedure for Mn(III) acetate**

A solution of 1 mmol indole or carbazole and 3 mmol Mn(OAc)₃ in 11 mL benzene–AcOH (10:1) was stirred under reflux (Dean–Stark apparatus) during which the dark brown color of Mn(OAc)₃ disappeared, which was monitored by TLC. After all the starting material was consumed, the reaction mixture was filtered through a pad of silica using ethyl acetate and then washed with brine. The resulting organic phase was dried over MgSO₄ and concentrated under vacuum. The crude products were purified by column chromatography using EtOAc–hexane as an eluent.

**1-Acetoxymethyl-1H-indole (2).** (106 mg, 56 %) red oil; Rf (EtOAc/Hexane 1:10) 0.60. IR (neat) νmax: 3048, 2926, 1744, 1610, 1463, 1333, 1186, 1014. ¹H NMR (400 MHz, CDCl₃) δ: 7.59 (1H, d, J = 7.9 Hz, ArH), 7.47 (1H, d, J = 8.2 Hz, ArH), 7.20-7.25 (2H, m, ArH), 7.13 (1H, t, J = 7.5 Hz, ArH), 6.50 (1H, d, J = 3.2 Hz, ArH), 6.05 (2H, s, OCH₂), 2.01 (3H, s, Me). ¹³C NMR (100 MHz, CDCl₃) δ: 170.3, 136.1, 129.1, 128.4, 122.5, 121.1, 120.7, 109.5, 103.7, 68.2, 20.7. Anal. Calcd. for C₁₁H₁₁NO₂ (189.21): C, 69.83; H, 5.86; N, 7.40. Found: C, 69.75; H, 5.91; N, 7.33.

**1-Methyl-2-phenyl-1H-indol-3-yl acetate (5).** (62 mg, 23 %) red oil; Rf (EtOAc/Hexane 1:10) 0.55. IR (neat) νmax: 3050, 2936, 1753, 1601, 1455, 1376, 1201. ¹H NMR (400 MHz, CDCl₃) δ:
7.31-7.41 (6H, m, ArH), 7.24 (1H, d, J= 8.4 Hz, ArH), 7.14 (1H, t, J= 7.4 Hz, ArH), 7.05 (1H, t, J= 7.4 Hz, ArH), 3.59 (3H, s, CH₃N), 2.17 (3H, s, CH₃COO). ¹³C NMR (100 MHz, CDCl₃) δ: 169.5, 135.0, 129.9, 129.6, 128.5, 128.2, 126.6, 122.4, 120.7, 120.0, 117.5, 109.7, 103.2, 30.9, 20.5. Anal. Calcd. for C₁₇H₁₅NO₂ (265.31): C, 76.96; H, 5.70; N, 5.28. Found: C, 76.82; H, 5.79; N, 5.18.

(2-Phenyl-1H-indol-1-yl)methyl acetate (6). (48 mg, 18 %) red oil; Rf (EtOAc/Hexane 1:10) 0.65. IR (neat) ν max: 3054, 2978, 1754, 1606, 1460, 1352, 1207. ¹H NMR (400 MHz, CDCl₃) δ: 7.34-7.53 (7H, m, ArH), 7.18 (1H, t, J= 7.6 Hz, ArH), 7.12 (1H, t, J= 7.4 Hz, ArH), 6.53 (1H, s, ArH), 6.03 (2H, s, OCH₂), 2.17 (3H, s, Me). ¹³C NMR (100 MHz, CDCl₃) δ: 170.0, 141.2, 137.7, 131.8, 129.4, 128.6, 128.5, 128.4, 122.7, 121.3, 120.6, 110.1, 104.3, 67.2, 20.9. Anal. Calcd. for C₁₇H₁₃NO₂ (265.31): C, 76.96; H, 5.70; N, 5.28. Found: C, 76.79; H, 5.61; N, 5.21.

1-[(Acetoxy)methyl]-2-phenyl-1H-indol-3-yl acetate (7). (146 mg, 45 %) red oil; Rf (EtOAc/Hexane 1:10) 0.45. IR (neat) ν max: 3054, 2958, 1744, 1602, 1457, 1331, 1222.

¹H NMR (400 MHz, CDCl₃) δ: 7.41-7.52 (7H, m, ArH), 7.28 (1H, t, J= 7.6 Hz, ArH), 7.18-7.25 (1H, m, ArH), 6.01 (2H, s, OCH₂), 2.23 (3H, s, CH₃COO), 2.03 (3H, s, CH₃COOCH₂N). ¹³C NMR (100 MHz, CDCl₃) δ: 169.9, 169.1, 134.6, 130.0, 129.7, 128.8, 128.6, 128.5, 128.2, 123.6, 121.8, 121.4, 117.7, 110.4, 66.9, 20.8, 20.4. Anal. Calcd. for C₁₉H₁₅NO₄ (323.34): C, 70.58; H, 5.30; N, 4.33. Found: C, 70.39; H, 5.41; N, 4.21.

1-Ethyl-2-phenyl-1H-indol-3-yl acetate (9). (185mg, 66 %) yellow solid (mp 119-120°C); Rf (EtOAc/Hexane 1:5) 0.50. IR (CHCl₃) ν max: 3052, 2968, 1740, 1605, 1455, 1335, 1227.

¹H NMR (400 MHz, CDCl₃) δ: 7.29-7.41 (7H, m, ArH), 7.15 (1H, t, J= 7.6 Hz, ArH), 7.06 (1H, t, J= 7.6 Hz, ArH), 4.03 (2H, q, J= 7.2 Hz, CH₂CH₃), 2.14 (3H, s, CH₃COO), 1.19 (3H, t, J= 7.2 Hz, CH₃CH₃). ¹³C NMR (100 MHz, CDCl₃) δ: 169.7, 133.8, 129.9, 129.8, 129.6, 128.6, 128.4, 126.7, 122.3, 121.0, 119.9, 117.6, 110.0, 38.7, 20.5, 15.3. Anal. Calcd. for C₁₉H₁₇NO₂ (279.33): C, 77.40; H, 6.13; N, 5.01. Found: C, 77.38; H, 6.19; N, 4.95.

Methyl 3-acetoxy-1-methyl-1H-indole-2-carboxylate (11). (110 mg, 44 %) yellow solid (mp 112-113°C); Rf (EtOAc/Hexane 1:5) 0.25. IR (CHCl₃) ν max: 3057, 2968, 1740, 1602, 1465. ¹H NMR (400 MHz, CDCl₃) δ: 7.45 (1H, d, J= 8.2 Hz, ArH), 7.28 (2H, d, J= 4.2 Hz, ArH), 7.07 (1H, pent., J= 3.8 Hz, ArH), 3.92 (3H, s, O-Me), 3.82 (3H, s, N-Me), 2.32 (3H, s, CH₃COO). ¹³C NMR (100 MHz, CDCl₃) δ: 169.3, 161.4, 136.6, 134.5, 126.0, 120.7, 119.5, 119.0, 117.4, 110.3, 51.7, 31.8, 20.6. Anal. Calcd. for C₁₃H₁₃NO₄ (247.25): C, 63.15; H, 5.30; N, 5.67. Found: C, 63.26; H, 5.15; N, 5.78.

Methyl 3-acetoxy-1-(acetoxymethyl)-1H-indole-2-carboxylate (12). ( 80 mg, 26 %) yellow oil; Rf(EtOAc/Hexane 1:10) 0.15. IR (neat) ν max: 3051, 2953, 1757,1552, 1473.

¹H NMR (400 MHz, CDCl₃) δ: 7.45-7.52 (1H, m, ArH), 7.35 (1H, t, J= 7.6 Hz, ArH), 7.13-7.18 (2H, m, ArH), 6.49 (2H, s, OCH₂N), 3.85 (3H, s, OMe), 2.34 (3H, s, CH₃COO), 1.97 (3H, s, CH₃COOCH₂N). ¹³C NMR (100 MHz, CDCl₃) δ: 170.4, 168.7, 160.8, 136.8, 128.2, 127.1122.0, 120.5, 119.2, 116.9, 110.9, 66.8, 51.9, 20.8, 20.6. Anal. Calcd. for C₁₅H₁₅NO₆ (305.28): C, 59.01; H, 4.95; N, 4.59. Found: C, 59.17; H, 4.88; N, 4.67.
{1-[(Acetyloxy)methyl]-1H-indol-2-yl}methyl acetate (15). (27 mg, 10 %) yellow oil \( R_f \) (EtOAc/Hexane 1:5) 0.30. IR (neat) \( \nu_{\text{max}} \): 3056, 2951, 1750, 1552, 1470. \(^1\)H NMR (400 MHz, CDCl\(_3\) ) \( \delta \): 7.52 (1H, d, \( J= 7.8 \) Hz, ArH), 7.44 (1H, d, \( J= 8.2 \) Hz, ArH), 7.18-7.23 (1H, m, ArH), 7.11 (1H, t, \( J= 7.6 \) Hz, ArH), 6.56 (1H, s, ArH), 6.11 (2H, s, OCH\(_2\)N), 5.28 (2H, s, OCH\(_2\) ), 2.01 (3H, s, CH\(_3\)COO CH\(_2\) ), 1.97 (3H, s, CH\(_3\)COOCH\(_2\)N). \(^{13}\)C NMR (100 MHz, CDCl\(_3\) ) \( \delta \): 170.3, 137.6, 133.6, 127.7, 123.4, 122.1, 121.1, 109.9, 106.7, 66.1, 57.7, 20.8, 20.7.

Anal. Calcd. for C\(_{14}\)H\(_{15}\)NO\(_4\) (261.27): C, 64.36; H, 5.79; N, 5.36. Found: C, 64.30; H, 5.88; N, 5.39.

(Acetyloxy)(1-methyl-1H-indol-2-yl)methyl acetate (16). (142 mg, 54 %) white solid (mp 114-115\(^0\)C); \( R_f \) (EtOAc/Hexane 1:5) 0.37. IR (CHCl\(_3\) ) \( \nu_{\text{max}} \): 3058, 2978, 1757, 1560, 1474, 1370. \(^1\)H NMR (400 MHz, CDCl\(_3\) ) \( \delta \): 7.89 (1H, s, CH(CH\(_3\)COO)\(_2\) ), 7.54 (1H, d, \( J= 7.9 \) Hz, ArH), 7.17-7.21 (1H, m, ArH), 7.04 (1H, t, \( J= 7.4 \) Hz, ArH), 6.64 (1H, s, ArH), 3.78 (3H,s, N-Me), 2.05 (2x3H, s, CH(CH\(_3\)COO)\(_2\) ). \(^{13}\)C NMR (100 MHz, CDCl\(_3\) ) \( \delta \): 168.2, 138.3, 132.7, 126.6, 123.0, 121.5, 120.0, 109.3, 103.3, 84.9, 30.7, 20.7.

Anal. Calcd. for C\(_{14}\)H\(_{15}\)NO\(_4\) (261.27): C, 64.36; H, 5.79; N, 5.36. Found: C, 64.30; H, 5.68; N, 5.43.

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