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Mn(III)-based radical addition reactions of 2-nitroindole with activated CH compounds

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ABSTRACT

2-Nitroindole undergoes addition reactions with the radicals generated from active CH compounds upon treatment with $Mn(OAc)_3 \cdot 2H_2O$ to afford the corresponding 3-substituted-2-nitroindoles in 27–66% yields. Products of the methylene addition reactions undergo a subsequent in situ Nef reaction to afford 2-oxoindolin-3-ylidenes.

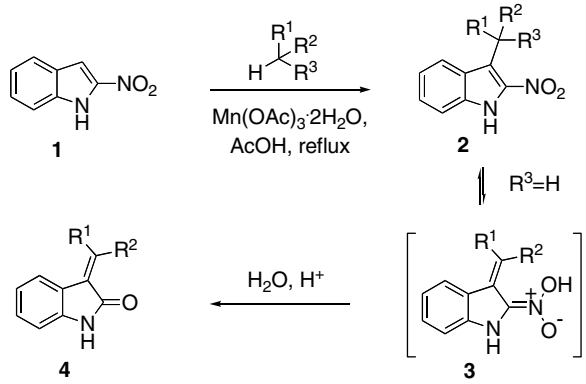
Over the past 40 years manganese(III)-promoted oxidative free-radical reactions have emerged as a powerful and versatile method for organic synthesis.[1] Recent applications include the tandem malonyl radical alkene addition and cyclization onto indole,[2] a catalytic-based addition of carboxyalkyl radicals to alkenes,[3] and the key step in the first total synthesis of mersicarpine,[4] to name but a few.

In continuation with our interest in the chemistry of 2- and 3-nitroindoles,[5] we now report that 2-nitroindole (**1**)[6] undergoes manganese(III) acetate-promoted radical addition reactions with activated methylene and methine compounds in refluxing acetic acid (Scheme 1). Our results are summarized in Table 1. Whereas the reactions of **1** with 3-methylpentane-2,4-dione and 5-oxo-4-propionylheptane-nitrile with $Mn(OAc)_3 \cdot 2H_2O$ (HOAc, reflux) afford the anticipated 3-substituted 2-nitroindoles **2a** and **2b**, respectively, the same reaction conditions with pentane-2,4-dione, malonitrile, dimethyl malonate, 1,3-diphenylpropane-1,3-dione, 1-phenylbutane-1,3-dione, and methyl 3-oxobutanoate unexpectedly give the corresponding 2-oxoindolin-3-ylidenes (**4a–f**), the products of an in situ Nef reaction[7] of intermediate **2.** Presumably, 2-nitroindole **2** undergoes tautomerization to a 2-*aci*-nitro species **3** followed by hydrolysis to **4**.

Our synthesis of **4** provides an alternative route to these 2-oxoindolin-3-ylidenes that typically involves condensation of isatin with activated methylene compounds.[8] It might be noted that some 2-oxoindolin-3-ylidenes demonstrate selective inhibition of tyrosine kinases,[9] and 3-methyleneindolin-2-one, which is a metabolite of indole-3-acetic acid, exhibits cytotoxicity and has potential for use in cancer therapy.[10] We had previously found that 2-nitro-1-(phenylsulfonyl)indole reacts with enolates of diethyl malonate and cyclohexanone (anionic addition) to give 3-alkyl-2-nitroindoles. However, those adducts are stable under the reaction conditions (NaH, THF, low temperature), and do not undergo a Nef reaction.[11]

Interestingly, 3-nitroindole is unreactive under these conditions ($Mn(OAc)_3 \cdot 2H_2O$, AcOH, reflux) with the same active CH compounds, which is perhaps due to the absence of a captodative stabilizing effect that the radical intermediate **A** generated from 2-nitroindole enjoys, whereas radical intermediate **B** does not (Fig. 1).

The structures of **2a–b** and **4a–f** are supported by spectral data (MS, NMR),[12] and the ^{1}H- and ^{13}C-NMR data are consistent with literature values for similar compounds.[13,14] Alkylidenes **4e,f**, which bear different substituents ($R^1 \neq R^2$), are obtained as mixtures of *E*- and *Z*-isomers. The stereochemistry at the C3–C8 double bond of isomeric **4e** could be deduced by comparison of the 1D-NOE



Scheme 1.

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Table 1
3-Alkyl-2-nitroindoles **2a–b** and 2-oxoindolin-3-ylidenes **4a–f** produced using $Mn(OAc)_3$ via Scheme 1[a]

Entry	Compound	R^1	R^2	R^3	Time (min)	Yield (%)
1	**2a**	CO(O)Me	CO(O)Me	Me	30	53
2	**2b**	C(O)Et	C(O)Et	$(CH_2)_2CN$	60	48
3	**4a**	C(O)Me	C(O)Me	H	15	52
4[b]	**4b**	CN	CN	H	60	66
5	**4c**	CO(O)Me	CO(O)Me	H	10	55
6	**4d**	C(O)Ph	C(O)Ph	H	30	49
7	**4e1** (*E*-isomer)	C(O)Ph	C(O)Me	H	15	27
8	**4e2** (*Z*-isomer)	C(O)Me	C(O)Ph			40
9[c]	**4f1** (*E*+*Z*) 1.7:1	CO(O)Me	C(O)Me	H	20	61
	4f2 (*E*+*Z*) 1.7:1	C(O)Me	CO(O)Me			

[a] For procedures see Ref. 12a.
[b] Literature data—Refs. 8d,13.
[c] The mixture of *E*- and *Z*-isomers.

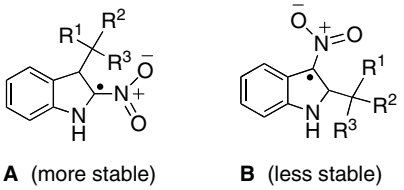

Figure 1. Relative stability of radicals **A** and **B**.

spectra of both isomers. Thus, irradiation of the methyl protons of **4e2** (*Z*-isomer) at $\delta_H = 2.64$ results in a significant NOE of H4 at $\delta_H = 8.15$; whereas irradiation of the methyl protons of **4e1** (*E*-isomer) at $\delta_H = 2.50$ results in no NOE of H4 at $\delta_H = 7.65$. In this isomer, the phenyl group is shielding H4 (Fig. 2). Similar NOE experiments were carried out on the mixture of **4f**: irradiation of the H-4 proton at $\delta_H = 8.21$ causes NOE on the protons of $CO(O)CH_3$ at $\delta_H = 3.90$, while irradiation of the H-4 proton at $\delta_H = 7.93$ results in an NOE of the protons of $C(O)CH_3$ $\delta_H = 2.48$. The latter result reveals that carbomethoxy deshields H4 more than acetyl does (Fig. 2).

As additional structural proof, we synthesized **4c** independently from isatin and dimethyl malonate using the Knoevenagel method reported by Jones.[8a]

Unfortunately, attempts to increase the yields by employing the co-oxidant $Cu(OAc)_2$ were unsuccessful and the yields of **4** were virtually unchanged.[12b] Copper acetate in conjunction with $Mn(OAc)_3$ is known to increase the rate of oxidation of the intermediate secondary radical (i.e., **A**).[1a,15]

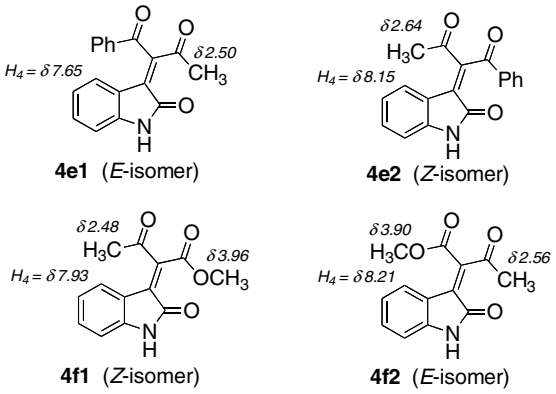

Figure 2. Structures of *E*- and *Z*-isomers of **4e** and **4f**.

In summary, we have described the Mn(III)-promoted free radical addition of active methylene compounds to 2-nitroindole followed by a spontaneous in situ Nef reaction to provide a novel synthesis of 2-oxoindolin-3-ylidenes, which have found recent utility in the synthesis of the maremycins,[16] spirocyclic 2-oxindoles,[17] new Cdc25 phosphatase inhibitors,[18] and β-carbolines.[19] In the case of active methine compounds the radical addition reaction affords the 2-nitro-3-substituted indole.

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12. (a) *General procedure for the synthesis of 3-alkyl-2-nitroindoles **2a-b** and 2-oxoindolin-3-ylidenes* **4a–f**. 2-Nitroindole (**1**) (0.05 g; 0.309 mmol), $Mn(OAc)_3 \cdot 2H_2O$ (5 equiv, 0.414 g, 1.543 mmol), and the corresponding methylene or methylidene compound (5 equiv, 1.543 mmol) and AcOH (10 mL) were charged into a 50 mL round bottom flask. The mixture was refluxed for 10–60 min. After completion of the reaction, water was added (200 mL) and the water phase was extracted with AcOEt (3 × 50 mL). The organic phase was washed with water (3 × 100 mL), the solvent was removed under reduced pressure, and the residue was purified via column chromatography (SiO_2, EtOAc/hexane (1:1) or (1:2)) to afford the corresponding 3-alkyl-2-nitroindole **2a–b** or 2-oxoindolin-3-ylidene **4a–f**. (for yields see Table 1. (b) *General procedure using $Cu(OAc)_2$ H_2O: 2-(2-Oxo-1,2-dihydroindol-3-ylidene)malonic acid dimethyl ester* **4c** (Procedure **B**): 2-Nitroindole (**1**) (0.05 g; 0.309 mmol), $Mn(OAc)_3 \cdot 2H_2O$ (5 equiv, 0.41 g, 1.543 mmol), $Cu(OAc)_2 \cdot H_2O$ (0.1 equiv, 0.006 g, 0.0309 mmol), $NaOAc \cdot 3H_2O$ (10 equiv, 0.42 g, 1.543 mmol), dimethyl malonate (5 equiv, 0.2 g, 1.543 mmol), and AcOH (10 mL) were charged into a 50 mL round bottom flask. The mixture was stirred and heated at 80 °C for 5 h. After completion of the reaction, water was added (200 mL) and the water phase was extracted with AcOEt (3 × 50 mL). The organic phase was washed with water (3 × 100 mL), the solvent was removed under reduced pressure, and the residue was purified via column chromatography (SiO_2, EtOAc/hexane (1:2)) to afford 38 mg of compound **4c** (47%) as an orange solid.
2-Methyl-2-(2-nitro-1H-indol-3-yl)malonic acid dimethyl ester **2a**: This was purified via column chromatography (SiO_2, EtOAc/hexane (1:2)) to give a yellow solid, 50 mg (53%), mp 120–122 °C. ^1H NMR (300 MHz, $CDCl_3$) δ 2.00 (s, 3H), 3.81 (s, 6H), 7.16–7.22 (m, 1H), 7.38–7.44 (m, 3H), 9.48 (br s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 22.0, 53.7, 55.4, 113.1, 117.1, 121.9, 122.9, 124.6, 128.7, 133.7, 170.5; *m/z* (EI^+ mode) 306 (M^+, 43%), 260 (100), 247 (20), 219 (8), 201 (40), 186 (69), 157 (17), 146 (20), 115 (27), 101 (10), 84 (16), 59 (33); HRMS (EI^+ mode) calcd for $C_{14}H_{14}N_2O_6M^+$ 306.0852, found 306.0852.

2-(2-Cyanoethyl)-2-(2-nitro-1H-indol-3-yl)malonic acid diethyl ester **2b**: This was purified via column chromatography (SiO_2, EtOAc/hexane (1:2)) to give a yellow solid, 55 mg (48%), mp 161–162 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.22 (t, 6H), 2.47 (t, 2H), 2.93 (t, 2H), 4.22 (m, 2H), 4.35 (m, 2H), 7.20 (m, 1H), 7.34–7.46 (m, 3H); ^{13}C NMR ($CDCl_3$) δ 14.1, 30.4, 58.2, 63.2, 111.9, 113.6, 119.4, 121.3, 123.2, 125.5, 128.6, 133.6, 138.7, 168.7 *m*/*z* (EI^+ mode) 373 (M^+, 15%), 327 (32), 299 (6), 271 (5), 254 (12), 225 (100), 199 (21), 169 (11), 156 (9), 132 (12), 105 (16), 77 (15); HRMS (EI^+ mode) calcd for $C_{18}H_{19}N_3O_6$ M^+ 373.1274, found 373.1273.

3-(2-Oxo-1,2-dihydroindol-3-ylidene)-2,4-dione **4a**: This was purified via column chromatography (SiO_2, EtOAc/hexane (1:2)) to give an orange solid, 37 mg (52%), mp 125–126 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.51 (s, 3H), 2.56 (s, 3H), 6.87 (d, 1H), 6.98 (t, 1H), 7.30 (t, 1H), 7.41 (d, 1H), 8.59 (br s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 30.3, 31.3, 77.3, 111.0, 919.8, 123.3, 125.3, 126.8, 132.4, 142.9, 149.0, 168.6, 198.8, 201.5; *m*/*z* (EI^+ mode) 229 (M^+, 76%), 214 (21), 187 (28), 172 (100), 159 (27), 144 (44), 130 (18), 116 (29), 89 (17); HRMS (EI^+ mode) calcd for $C_{13}H_{11}NO_3$ M^+ 229.0739, found 229.0737.

2-(2-Oxo-1,2-dihydroindol-3-ylidene)malonitrile **4b**: This was purified via column chromatography (SiO_2, EtOAc/hexane (1:1)) to give a red solid, 40 mg (66%), mp 228–229 °C (lit.[8d] mp 235–238 °C). ^{1}H NMR (300 MHz, DMSO-d_6) δ 6.91 (d, 1H), 7.11 (t, 1H), 7.55 (t, 1H), 7.85 (d, 1H), 11.2 (s, 1H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 80.6, 111.56, 111.64, 113.1, 118.8, 122.9, 125.9, 137.8, 146.5, 150.7, 163.8.

2-(2-Oxo-1,2-dihydroindol-3-ylidene)malonic acid dimethyl ester **4c**: This was purified via column chromatography (SiO_2, EtOAc/hexane (1:1)) to give an orange solid, 44 mg (55%), mp 141–142 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.92 (s, 3H), 3.95 (s, 3H), 6.82 (d, 1H), 7.04 (t, 1H), 7.34 (t, 1H), 7.93 (br s, 1H), 8.39 (d, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 53.4, 53.5, 110.4, 119.9, 123.3, 129.0, 129.5, 133.7, 135.4, 143.6, 163.5, 166.3, 167.5; *m*/*z* (EI^+ mode) 261 (M^+, 100%), 230 (70), 202 (23), 170 (46), 162 (17), 143 (27), 130 (21), 115 (24), 88 (15); HRMS (EI^+ mode) calcd for $C_{13}H_{11}NO_5$ M^+ 261.0637, found 261.0639.

2-(2-Oxo-1,2-dihydroindol-3-ylidene)-1,3-diphenylpropane-1,3-dione **4d**: This was purified via column chromatography (SiO_2, EtOAc/hexane (1:2)) to give an orange amorphous solid, 53 mg (49%), mp 93–95 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.72 (d, 1H), 6.79 (t, 1H), 6.95 (d, 1H), 7.19 (t, 1H), 7.47–7.67 (m, 5H), 8.09 (d, 1H), 8.18 (d, 2H), 8.28 (d, 2H), 8.77 (br s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 111.1, 119.8, 122.9, 124.7, 128.7, 128.93, 128.97, 129.4, 130.1, 130.3, 131.1, 131.6, 133.8, 134.3, 134.4, 135.4, 135.6, 142.6, 147.9, 167.8, 192.1, 192.2; *m*/*z* (EI^+ mode) 353 (M^+, 19%), 296 (4), 248 (7), 220 (6), 122 (45), 105 (100), 84 (86); HRMS (EI^+ mode) calcd for $C_{23}H_{15}NO_3$ M^+ 353.1052, found 353.1053.

(E)-2-(2-Oxo-1,2-dihydroindol-3-ylidene)-1-phenylbutane-1,3-dione **4e1**: This was purified via column chromatography (SiO_2, $CHCl_3$/hexane (1:2)) to give an orange amorphous solid, 24 mg (27%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.50 (s, 3H), 6.78 (d, 1H), 7.03 (t, 1H), 7.31 (t, 1H), 7.44–7.52 (m, 2H), 7.56–7.68 (m, 2H), 8.00–8.12 (m, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 30.2, 110.8, 119.9, 123.1, 125.6, 128.7, 129.16, 129.23, 130.4, 132.5, 133.8, 134.3, 136.1, 143.1, 147.4, 168.0, 193.9, 198.6; HRMS (EI^+ mode) calcd for $C_{18}H_{13}NO_3$ M^+ 291.0896, found 291.0894.

(Z)-2-(2-Oxo-1,2-dihydroindol-3-ylidene)-1-phenylbutane-1,3-dione **4e2**: This was purified via column chromatography (SiO_2, $CHCl_3$/hexane (1:2)) to give an orange amorphous solid, 36 mg (40%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.64 (s, 3H), 6.78 (m, 2H), 6.86 (d, 1H), 7.18 (t, 1H), 7.44–7.52 (m, 3H), 7.62–7.70 (m, 1H), 8.10–8.20 (m, 2H), 8.71 (br s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 30.8, 111.0, 119.9, 123.0, 124.8, 128.7, 129.6, 130.4, 130.7, 131.5, 133.9, 134.3, 135.5, 142.4, 149.4, 168.3, 192.0, 199.9; *m*/*z* (EI^+ mode) 291 (M^+, 11%), 220 (6), 122 (33), 105 (58), 84 (100); HRMS (EI^+ mode) calcd for $C_{18}H_{13}NO_3$ M^+ 291.0896, found 291.0894.

(E)- and (Z)-3-Oxo-2-(2-Oxo-1,2-dihydroindol-3-ylidene)butyric acid methyl ester (mixture E:Z-1.7:1) **4f**: This was purified via column chromatography (SiO_2, EtOAc/hexane (1:1)) to give an orange amorphous solid, 46 mg (61%). *Z*-isomer (**4f1**): ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.48 (s, 3H), 3.96 (s, 3H), 6.82 (d, 1H), 6.98 (t, 1H), 7.32 (t, 1H), 7.93 (d, 1H), 8.49 (br s, 1H). *E*-isomer (**4f2**): ^{1}H NMR (300 MHz, CDCl3) δ 2.56 (s, 3H), 3.90 (s, 3H), 6.86 (d, 1H), 7.03 (t, 1H), 7.32 (t, 1H), 8.21 (d, 1H), 8.57 (br s, 1H).

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