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Manganese(III)-mediated oxidative radical addition of malonates to 2-cyanoindoles

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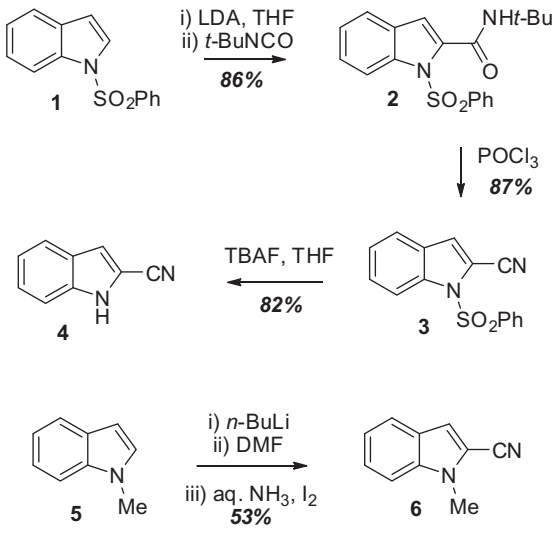
ABSTRACT

2-Cyanoindole and N-methyl-2-cyanoindole undergo manganese(III)-mediated radical addition with activated methylene and methine compounds. Products of the methylene addition underwent additional oxidation during the course of the reaction to furnish the corresponding acetoxy compounds. Several structures were confirmed by X-ray crystallography.

Since the seminal reports disclosing the manganese(III) acetate-promoted oxidative addition of acetic acid to alkenes in 1968,[1] manganese(III)-based free-radical reactions continue to find new applications in organic synthesis.[2] In just the last few years, new reports include the synthesis of sterically congested cyclopentane-lactones,[3] (Z)-selective exo-alkylidene pyrrolidinones and pyrrolidines,[4] trifluoromethylated dihydrofurans,[5] 2-thienyl-substituted dihydrofurans,[6] and fluoroacylated 4,5-dihydrofurans.[7]

Given our longstanding interest in the chemistry of electron-deficient indoles,[8] we previously reported the manganese(III) acetate-promoted radical addition of activated methylene and methine compounds to 2-nitroindoles which furnish either the corresponding 3-substituted-2-nitroindoles or 2-oxoindolin-3-ylidenes; the latter product is isolated after an in situ Nef reaction.[9] In order to expand this methodology, we began to investigate cyanoindoles as possible substrates for the radical additions. The cyano group provides an orthogonal chemical handle for further elaboration when compared to the nitro group, and would circumvent the Nef reaction seen previously.

According to a literature procedure, N-phenylsulfonyl-2-cyanoindole (**3**) was prepared in two steps from **1** by installation of the amide with t-butyl isocyanate (**2**) followed by treatment with phosphorus oxychloride.[10] Deprotection with TBAF delivered 2-cyanoindole (**4**) in good yield while avoiding hydrolysis of the nitrile which has been observed with other bases.[11,12] 2-Cyano-N-methylindole (**6**) was synthesized in one-pot via sequential addition of n-butyllithium, DMF, and aqueous ammonia/I_2 to **5** (Scheme 1).[13] With these compounds in hand, as well



Scheme 1. Preparation of 2-cyanoindoles.

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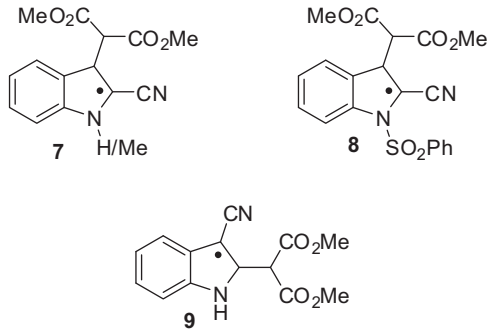
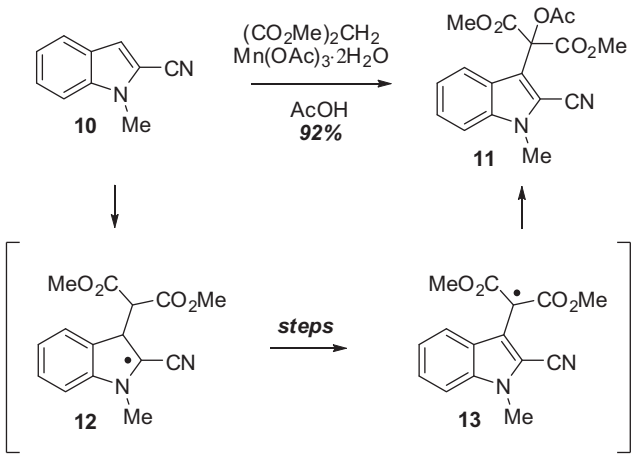


Figure 1. Possible radicals generated on 2- and 3-cyanoindoles.



Scheme 2. Radical addition to cyanoindole **10** via captodative radical **12** and malonate radical **13**.

as the analogous 3-cyano compounds, we screened the indole substrates under our standard radical addition conditions.[9]

The 3-cyanoindoles were unreactive, returning only starting material. The same was true of N-phenylsulfonyl-2-cyanoindole (**3**). This falls in line with our previous observations of nitroindoles and can be explained by the captodative effect.[14] Addition of malonate to the indole requires a stabilized radical be formed at either -2 C-2 or -3. C-3. The more stable radical **7** will be located on the carbon which has both an electron-withdrawing and electron-donating group immediately attached (in this case, at -2). C-2). Moreover, installation of the phenylsulfonyl group on nitrogen withdraws enough electron density from -2 C-2 that the captodative effect is eliminated in **8** (Fig. 1).

Optimum yields were obtained with either unprotected indole **4** or N-methylindole **6** and $Mn(OAc)_3{\cdot}2H_2O$ in refluxing acetic acid. The addition of copper(II) acetate as a co-oxidant did not have a noticeable effect on either the yield or rate. If the initial product (**12**) still contains an enolizable malonate proton, a second radical was generated (**13**) by the deprotonation of the remaining C–H bond, oxidation of the resulting enolate, and trapping with acetate.[2] This second oxidation proved unavoidable during the course of the reaction (Scheme 2).[15]

A variety of unsubstituted and monosubstituted malonate-type compounds successfully engaged in the radical reaction (Table 1) in moderate to good yields, although reaction times were noticeably longer than was observed with the corresponding nitroindoles. It is noteworthy that when diethyl bromomalonate is used as a reaction partner (Table 1, entry **6**), the bromide is displaced by acetate to furnish **18** as the final product. This stands in contrast to previous examples in the literature where the bromide remains in the isolated radical addition product.[16] Single crystals were obtained for products **14**, **15**, and **16** which also serves to confirm the uptake of acetate with unsubstituted malonates (Fig. 2).

In conclusion, we have developed the Mn(III)-based oxidative free radical addition of malonate-type compounds to 2-cyanoindoles in moderate to good yields. This approach provides a complementary substrate set to our nitroindole chemistry and expands the possibilities for further elaboration of the indole radical addition products.

Acknowledgments

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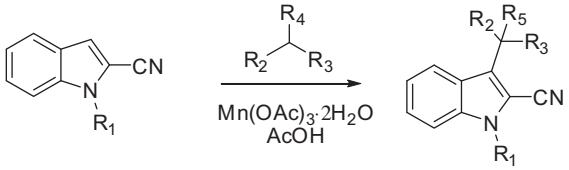
Table 1
Scope of radical additions[17–25]



Entry	R^1	R^2	R^3	R^4	R^5	Time (h)	Compd[18–25]	Yield (%)[a]
1	Me	CO_2Me	CO_2Me	Me	Me	2	**14**	91 (63)[b]
2	Me	CO_2Et	CO_2Et	H	OAc	2	**15**	90 (73)[b]
3	Me	CO_2Et	CO_2Et	$(CH_2)_2CN$	$(CH_2)_2CN$	2	**16**	78 (71)[b]
4	Me	CO_2Me	CO_2Me	H	OAc	4	**11**	92 (57)[b]
5	H	CO_2Et	CN	Me	Me	24	**17**	58
6	H	CO_2Et	CO_2Et	Br	OAc	4	**18**	72
7	H	CO_2Me	COMe	H	OAc	4	**19**	67
8	H	CO_2Me	CO_2Me	H	OAc	1.5	**20**	81
9	H	CO_2Et	CO_2Et	Ph	Ph	48	**21**	0

[a] For general procedure, see note **17a**.
[b] Yield from reactions with $Cu(OAc)_2{\cdot}2H_2O$ as co-oxidant, see note **17b**.

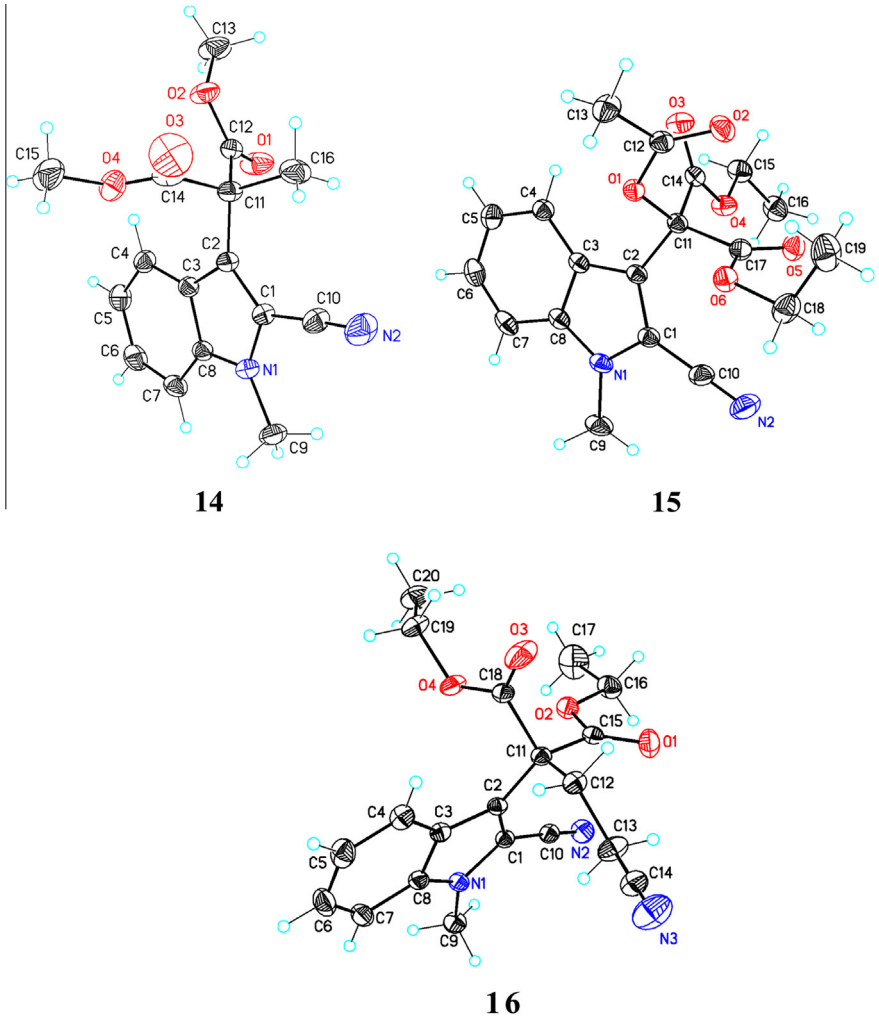


Figure 2. ORTEP diagrams of radical addition products **14**, **15,** and **16**.

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12. *2-Cyanoindole* ***4****:* To a solution of N-phenylsulfonyl-2-cyanoindole (**3**, 2.0 g, 7.1 mmol, 1 equiv) in THF (30 mL) was added a solution of TBAF (10.6 mL, 1.0 M in THF, 1.5 equiv). After heating at reflux for 3 h, the mixture was cooled to room temperature and concentrated in vacuo. The residue was dissolved in ethyl acetate (100 mL) and water (100 mL) and the layers separated. The organic layer was washed with brine, dried over Na_2SO_4, and concentrated in vacuo to an off-white solid. The product was purified by flash chromatography (silica gel, hexanes:EtOAc 4:1) to afford **4** as a white solid, 827 mg (82%); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.66 (br s, 1H), 7.68 (d, 1H, J = 8.1 Hz), 7.44–7.36 (m, 2H), 7.25–7.20 (m, 2H).[11]
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17. *General procedure for the synthesis of 3-substituted-2-cyanoindoles:* Cyanoindole **6** (40 mg, 0.256 mmol, 1 equiv.), $Mn(OAc)_3{\cdot}2H_2O$ (345 mg, 1.29 mmol, 5 equiv), and diethyl malonate (205 mg, 1.28 mmol, 5 equiv) were dissolved in acetic acid (10 mL) and heated to reflux for 2 h. After TLC indicated complete consumption of the starting indole, the reaction was poured into water (200 mL) and extracted with ethyl acetate (3 × 50 mL). The combined organic extracts were washed with water (3 × 100 mL), brine (1 × 100 mL), dried over sodium sulfate, filtered, and concentrated in vacuo to give a brown oil. The product was purified via flash chromatography (silica gel, hexanes:EtOAc 4:1) to afford **15** as a white solid (90%);[20]
General procedure for the synthesis of 3-substituted-2-cyanoindoles with co-oxidant: Cyanoindole **6** (40 mg, 0.256 mmol, 1 equiv), $Mn(OAc)_3{\cdot}2H_2O$ (345 mg, 1.29 mmol, 5 equiv), diethyl malonate (205 mg, 1.28 mmol, 5 equiv), $Cu(OAc)_2{\cdot}2H_2O$ (5 mg, 0.025 mmol, 0.1 equiv), and $NaOAc{\cdot}3H_2O$ (350 mg, 2.57 mmol, 10 equiv) were dissolved in acetic acid (10 mL) and heated to reflux for 2 h. After TLC indicated complete consumption of the starting indole, the reaction was poured into water (200 mL) and extracted with ethyl acetate (3 × 50 mL). The combined organic extracts were washed with water (3 × 100 mL), brine (1 × 100 mL), dried over sodium sulfate, filtered, and concentrated in vacuo to give a brown oil. The product was purified via flash chromatography (silica gel, hexanes:EtOAc 4:1) to afford **15** as a white solid (73%).

18. *Dimethyl 2-acetoxy-2-(2-cyano-1-methyl-1H-indol-3-yl)malonate* ***11****:* The product was purified via flash chromatography (silica gel, hexanes:EtOAc 4:1) to afford **11** as a white solid, 111 mg (92%), mp 138–140 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.85 (d, 1H, J = 8.5 Hz), 7.46–7.33 (m, 2H), 7.26–7.21 (m, 1H), 3.92 (s, 3H), 3.81 (s, 6H), 2.35 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.7, 165.8, 138.0, 126.5, 123.8, 122.4, 122.4, 117.7, 112.7, 110.5, 109.4, 80.8, 53.8, 31.9, 20.6; HRMS (ESI$^+$) calcd for $C_{17}H_{16}N_2O_6Na$ (MNa^+) 367.0906, found 367.0899.
19. *Dimethyl 2-(2-cyano-1-methyl-1H-indol-3-yl)-2-methylmalonate* ***14****:* The product was purified via flash chromatography (silica gel, hexanes:EtOAc 4:1) to afford **14** as a white solid, 49 mg (63%), mp 124–125 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.51 (d, 1H, J = 8.3 Hz), 7.43–7.32 (m, 2H), 7.18 (t, 1H, J = 6.8 Hz), 3.88 (s, 3H), 3.81 (s, 6H), 2.11 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.9, 138.1, 126.1, 124.9, 122.9, 122.1, 121.6, 113.4, 110.6, 108.8, 54.9, 53.4, 31.7, 23.0; HRMS (ESI$^+$) calcd for $C_{16}H_{17}N_2O_4$ (MH^+) 301.1188, found 301.1190. Single crystals suitable for X-ray crystallography were grown from 100% ethanol.
20. *Diethyl 2-acetoxy-2-(2-cyano-1-methyl-1H-indol-3-yl)malonate* ***15****:* The product was purified via flash chromatography (silica gel, hexanes:EtOAc 4:1) to afford **15** as a white solid, 70 mg (90%), mp 91–93 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.90 (d, 1H, J = 8.3 Hz), 7.44–7.32 (m, 2H), 7.26–7.19 (m, 1H), 4.31–4.27 (m, 4H), 3.91 (s, 3H), 2.35 (s, 3H), 1.30–1.21 (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.6, 165.2, 138.1, 126.4, 123.8, 122.8, 122.2, 117.7, 112.8, 110.4, 109.4, 80.4, 63.1, 31.8, 20.6, 14.1; HRMS (ESI$^+$) calcd for $C_{19}H_{20}N_2O_6Na$ (MNa^+) 395.1219, found 395.1223. Single crystals suitable for X-ray crystallography were grown from 100% ethanol.
21. *Diethyl 2-(2-cyano-1-methyl-1H-indol-3-yl)-2-(2-cyanoethyl)malonate* ***16****:* The product was purified via flash chromatography (silica gel, hexanes:EtOAc 4:1) to afford **16** as a white solid, 67 mg (71%), mp 104–106 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.46–7.36 (m, 2H), 7.23–7.18 (m, 1H), 4.44–4.24 (m, 4H), 3.92 (s, 3H), 2.82 (t, 2H, J = 7.6 Hz), 2.38 (t, 2H, J = 7.6 Hz), 1.27 (t, 6H, J = 7.1 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.6, 138.1, 126.6, 124.6, 122.1, 121.4, 119.3, 119.1, 112.8, 111.0, 109.9, 74.0, 63.1, 58.0, 32.0, 31.6, 14.0, 13.9; HRMS (ESI$^+$) calcd for $C_{20}H_{22}N_3O_4$ (MH^+) 368.1610, found 368.1612. Single crystals suitable for X-ray crystallography were grown from 100% ethanol.
22. *Ethyl 2-cyano-2-(2-cyano-1H-indol-3-yl)propanoate* ***17****:* The product was purified via flash chromatography (silica gel, hexanes:EtOAc 3:1) to afford **17** as a pale yellow oil, 55 mg (58%); ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.14 (br s, 1H), 7.93 (d, 1H, J = 9.0 Hz), 7.44–7.42 (m, 2H), 7.30–7.25 (m, 1H), 4.37–4.29 (m, 2H), 2.30 (s, 3H), 1.39–1.33 (m, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 165.8, 136.8, 135.4, 127.2, 124.1, 122.7, 122.4, 120.9, 116.6, 112.4, 109.9, 64.4, 49.0, 20.4, 14.1; HRMS (ESI$^+$) calcd for $C_{15}H_{13}N_3O_2Na$ (MNa^+) 290.0905, found 290.0903.
23. *Diethyl 2-acetoxy-2-(2-cyano-1H-indol-3-yl)malonate* ***18****:* The product was purified via flash chromatography (silica gel, hexanes:EtOAc 4:1) to afford **18** as a light yellow solid, 91 mg (72%), mp 124–126 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.66 (br s, 1H), 7.89 (d, 1H, J = 8.3 Hz), 7.41–7.31 (m, 2H), 7.22-7.16 (m, 1H), 4.32–4.24 (m, 4H), 2.35 (s, 3H), 1.26–1.20 (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.8, 165.2, 136.9, 126.5, 123.7, 122.2, 122.1, 118.6, 113.4, 112.2, 105.4, 80.4, 63.2, 20.5, 13.9; HRMS (ESI$^+$) calcd for $C_{18}H_{18}N_2O_6Na$ (MNa^+) 381.1063, found 381.1055.
24. *Methyl 2-acetoxy-2-(2-cyano-1H-indol-3-yl)-3-oxobutanoate* ***19***: The product was purified via flash chromatography (silica gel, hexanes:EtOAc 5:1) to afford **19** as a light orange solid, 74 mg (67%), mp 132–134 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.72 (br s, 1H), 7.70 (d, 1H, J = 8.3 Hz), 7.42–7.34 (m, 2H), 7.26–7.18 (m, 1H), 3.88 (s, 3H), 2.36 (s, 3H), 2.28 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 196.7, 170.4, 166.7, 137.1, 126.5, 123.8, 122.9, 122.1, 117.4, 113.2, 112.5, 105.6, 85.8, 53.6, 26.4, 20.7; HRMS (ESI$^+$) calcd for $C_{16}H_{14}N_2O_5Na$ (MNa^+) 337.0800, found 337.0791.
25. *Dimethyl 2-acetoxy-2-(2-cyano-1H-indol-3-yl)malonate* ***20****:* The product was purified via flash chromatography (silica gel, hexanes:EtOAc 5:1) to afford **20** as a white solid, 94 mg (81%), mp 145–147 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.64 (br s, 1H), 7.84 (d, 1H, J = 8.3 Hz), 7.42–7.33 (m, 2H), 7.26–7.18 (m, 1H), 3.81 (s, 6H), 2.36 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.1, 165.9, 137.0, 126.8, 123.8, 122.6, 121.9, 118.4, 113.4, 112.4, 105.5, 80.8, 54.0, 20.6; HRMS (ESI$^+$) calcd for $C_{16}H_{14}N_2O_6Na$ (MNa^+) 353.0750, found 353.0740.