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Oxidative and dehydrative cyclizations of nitroacetate esters with $Mn(OAc)_3$

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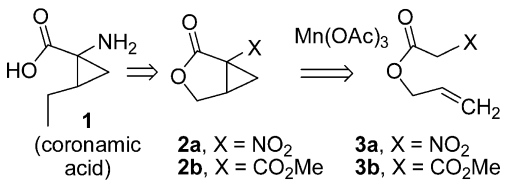
Abstract—Reaction of α-unsubstituted nitroacetates with $Mn(OAc)_3$ gives mixtures of isoxazolines, formed by dehydration to a nitrile oxide that undergoes cycloaddition, and isoxazoline oxides or cyclopropane, formed by oxidative cyclization. Oxidative cyclization is favored with electron-rich alkenes and cycloaddition with the nitrile oxide to give isoxazolines is favored with electron-poor alkenes. On the other hand, α-substituted nitroacetates cannot dehydrate and undergo only radical reactions.

1. Introduction

We have extensively developed $Mn(OAc)_3$-based oxidative free-radical cyclizations of unsaturated carbonyl and dicarbonyl compounds as a versatile procedure for generating a radical that can cyclize by enolization and oxidation of the enolate.[1] We envisaged that oxidative cyclization of unsaturated nitroacetates could provide a valuable route to highly functionalized amino acid precursors. For instance, coronamic acid (**1**)[2] should be accessible by straightforward manipulation of cyclopropane **2a**, which should be available by oxidative cyclization of allyl nitroacetate (**3a**). The analogous cyclization of allyl methyl malonate (**3b**) to afford 42% of cyclopropane **2b** was reported by Bertrand (Scheme 1).[3]



Scheme 1.

Oxidations of aci-nitro enolates to α-nitroalkyl radicals that add to alkenes have been extensively studied by Narasaka,[4] Bowman,[5] and Dulcère.[6] Chuang and co-workers reported $Mn(OAc)_3$-initiated oxidative free-radical reactions of ethyl nitroacetate with 1,4-naphthoquinones.[7] Warinsky and Strekhan reported free-radical additions of α-nitro ketones and α-nitroamides to alkenes mediated by $Mn(OAc)_3$.[8]

2. Results and discussion

Allyl nitroacetate (**3a**) was prepared in 67% yield by DCC-coupling of nitroacetic acid[9] with allyl alcohol as described by Mioskowski.[10] Reaction of **3a** with 2 equiv. of $Mn(OAc)_3$, 1 equiv. of $Cu(OAc)_2$, and 2 equiv. of NaOAc in HOAc at 90°C for 45 min yields only 7% (9% based on recovered **3a**) of the expected nitrocyclopropane **2a**.[11] To our surprise, the major product, formed in 38% yield (48% yield based on recovered **3a**) is the bicyclic isoxazoline **7** resulting from a dehydrative cyclization, rather than the expected isoxazoline oxide **8**, which could be formed by an oxidative cyclization. The structure of **7** was therefore carefully established. The spectral data and melting point are identical to those of an authentic sample.[15] The HRMS is consistent with isoxazoline **7**, not oxide **8**. The most significant difference between isoxazolines and isoxazoline oxides is the ^{13}C NMR chemical shift of the C=N carbon which absorbs at δ 150–160 in isoxazolines and 105–120 in isoxazoline oxides.[16] The C=N carbon (C-6a) of **7** absorbs at δ 156.5.

Reaction of **3a** with $Mn(OAc)_3$ should generate enolate **4**. Because the oxidation potential of **4** is large, the slow step in the formation of **2a** should be cyclization of **4** with loss of $Mn(OAc)_2$ to give radical **6**.[17] Oxidation and cyclization of **6** with $Cu(OAc)_2$ will give cyclopropane **2a**. Although oxidation and cyclization of **6** could also give isoxazoline oxide **8**, this reaction apparently does not occur. Loss of $Mn(OAc)_2OH$ from enolate **4** will give nitrile oxide **5**, which is known to undergo a dipolar cycloaddition to give isoxazoline **7** (Scheme 2).[15]

The formation of isoxazoline **7** from nitroacetate **3a** is a net dehydration, not an oxidation. We established that **7** is not formed from **3a** in HOAc containing NaOAc at 90°C.

Keywords: nitrile oxide; radical; isoxazoline; cyclization; cycloaddition.

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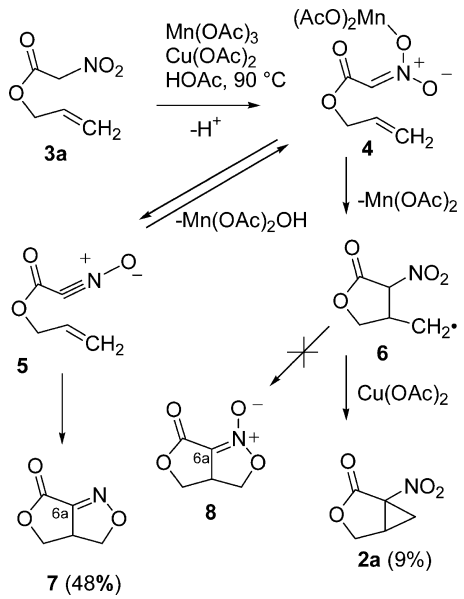
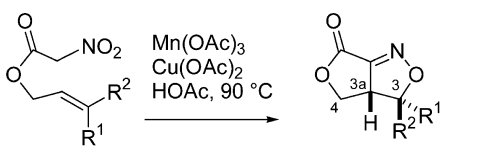


Scheme 2.

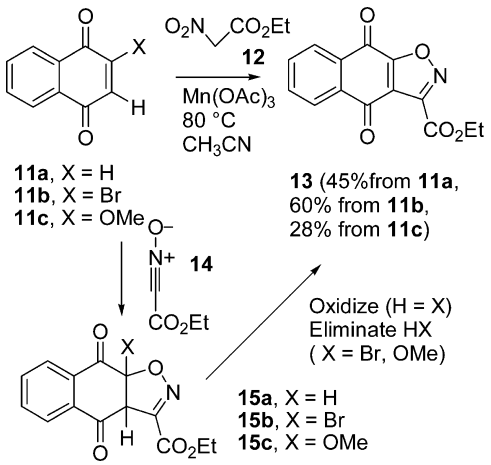
Reaction of **3a** in HOAc containing NaOAc and $Cu(OAc)_2$ affords 24% of **7**. These results indicate that $Cu(OAc)_2$ and $Mn(OAc)_3$ are acting as dehydrating agents in the formation of **7** from **3a**. $Mn(OAc)_3$ has recently been reported to be an effective dehydrating agent in the Biginelli condensation.[18] We also found that heating **3a** with $Co(OAc)_2$ and NaOAc in HOAc at 90°C affords 35% of **7** and no **2a**, indicating that metal acetate salts that are not oxidants can also effectively catalyze the dehydration of nitroacetate esters to nitrile oxides.

If the formation of **7** is occurring by a dipolar cycloaddition, addition to the double bond should be concerted and the double bond stereochemistry will be preserved in the product. We confirmed that this is the case by preparing **9a** and **9b** analogously to **3a**. Reaction of **9a** under the conditions used for cyclization of **3a** affords 49% of **10a** stereospecifically, while **9b** provides 60% of **10b**. The regiospecific cycloaddition provides further support for a mechanism involving a concerted cycloaddition. The stereochemistry of **10** was established by comparison of the ^{13}C NMR spectra. Carbons-3, 3a, 4 and the ethyl CH_2 group are shifted upfield in **10a** by 2–5 ppm from their position in **10b** due to the γ-*gauche* interaction between carbon-4 and the ethyl CH_2 group in **10a** (Scheme 3).



Scheme 3.

We do not wish to suggest that reaction of nitroacetates with $Mn(OAc)_3$ is the best method to generate nitrile oxides, which can be accomplished by numerous other methods.[19–26] It is, however, important to be aware of this mode of reaction of nitroacetates and $Mn(OAc)_3$. For instance, Chuang reported the formation of **13** from ethyl nitroacetate (**12**), $Mn(OAc)_3$ and naphthoquinones **11a–c** in the yields indicated and explained his results by a mechanism starting with oxidation of ethyl nitroacetate to a radical that adds to the quinone (Scheme 4).[7]



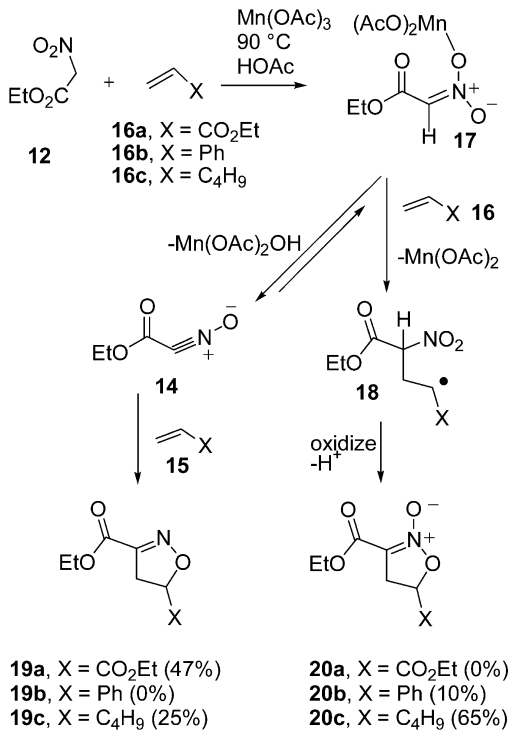
Scheme 4.

The formation of **13** from **11b** or **11c** is not an oxidation so that the proposed mechanism cannot be correct for these substrates. Dehydration of ethyl nitroacetate (**12**) will give nitrile oxide **14**, which will undergo a well-precedented[27,28] cycloaddition to naphthoquinones **11b** and **11c**, to give adducts **15b** or **15c**, respectively. Loss of HBr or HOMe will give **13**. Similarly, nitrile oxide **14** will add to **11a** to give **15a**, which will undergo a facile oxidation to generate quinone **13**.[27,28]

We also examined the intermolecular reaction of ethyl nitroacetate (**12**), $Mn(OAc)_3$ and ethyl acrylate, styrene or 1-hexene in HOAc at 90°C. In the absence of any alkene we isolated 25% of diethyl 1,2,3-oxadiazole-3,4-dicarboxylate oxide,[29] the known dimer of nitrile oxide **14**, and 60% of recovered **12**. Reaction with ethyl acrylate gives exclusively isoxazoline **19a** in 47% yield. The spectral data is identical to that reported;[23,25] the C=N carbon absorbs at δ 159.8. On the other hand, reaction with styrene proceeds with extensive oligomerization to give 10% of isoxazoline oxide **20b**,[30] and none of isoxazoline **19b** (Scheme 5).[31]

Reaction of ethyl nitroacetate with 1-hexene gives 25% of isoxazoline **19c** and 65% of isoxazoline oxide **20c**. The exact ratio of products varies with the reaction conditions. Lower temperatures and excess 1-hexene favor the formation of **19c**; at higher temperatures, **20c** decomposes slowly. The spectral data for isoxazoline **19c** are very similar to those of related isoxazolines with longer alkyl chains.[32,33] The C=N carbon absorbs at δ 151.3 in **19c** and δ 108.5 in isoxazoline oxide **20c**. The structure assignments were confirmed by HRMS. Lastly, deoxygenation of **20c** by refluxing in $P(OEt)_3$[34,35] affords **19c** quantitatively.

The divergent behavior of these alkenes can be understood in terms of their electronic character. Reaction of ethyl nitroacetate (**12**) with $Mn(OAc)_3$ should give manganese enolate **17**, which will react most rapidly with electron-rich



Scheme 5.

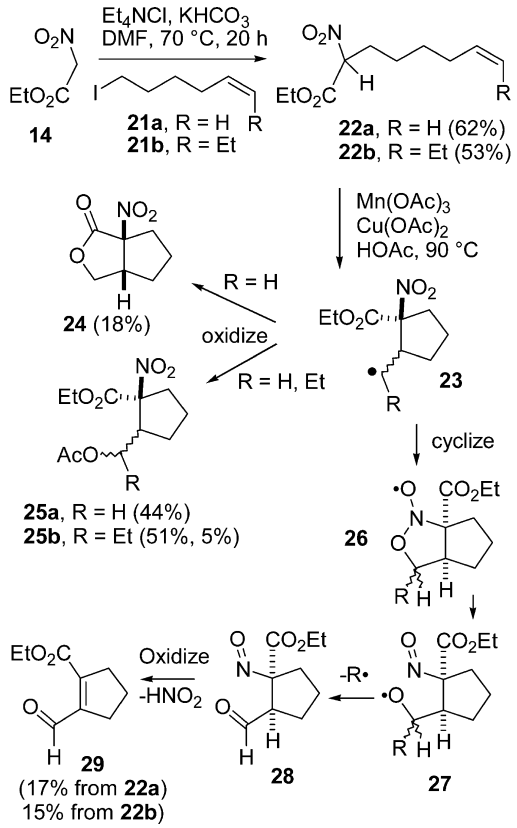
alkenes like styrene to give radical **18** and more slowly with electron-poor alkenes like ethyl acrylate. Loss of $Mn(OAc)_2OH$ will occur at a rate independent of the alkene to generate nitrile oxide **14**, although this step may be reversible. Therefore isoxazoline **19a** should be formed exclusively from electron-poor alkenes like ethyl acrylate and isoxazoline oxide **20b** should be formed exclusively from electron-rich alkene styrene. Both products are formed from 1-hexene.

This mechanistic scheme allows us to explain Warinksy and Strekhan's results in the additions of α-nitro ketones and amides to alkenes with $Mn(OAc)_3$.[8] They found that α-nitroacetophenone reacts with several alkenes to give isoxazoline oxides corresponding to **20** with a benzoyl group, rather than an ethyl ester. Their spectral data indicate that this is correct for all compounds except the most electron-poor alkene, allyl acetate, which gives a product that is an isoxazoline analogous to **19** based on the C=N carbon absorption at δ 157.4. The C=N carbon of all the other adducts absorbs between δ 115–120. They also found that reaction of the pyrrolidine amide of nitroacetic acid with 1-hexene and $Mn(OAc)_3$ gives a mixture of isoxazoline and isoxazoline oxide analogous to **19** and **20**. Their structure assignments based on HRMS appears to be switched based on the reported shift of the C=N carbon of the isoxazoline δ 112.4 and the isoxazoline oxide at δ 154.9. These results indicate that nitroacetate esters and nitroacetamides behave similarly, while the Mn(III) enolate of α-nitroacetophenone either undergoes radical reaction with alkenes more rapidly or forms the nitrile oxide more slowly than the nitro esters or amides.

We also examined intramolecular reactions of α-alkenyl nitroacetate esters. Alkylation[36] of ethyl nitroacetate (**12**) with iodoalkenes **21a** and **21b** in DMF with Et_4NCl and $KHCO_3$ at 70°C provides **22a** (62%) and **22b** (53%), respectively. Oxidation of **22a** with 2 equiv. of $Mn(OAc)_3$, and 1 equiv. of $Cu(OAc)_2$ and NaOAc in HOAc at 90°C for 55 min provides 18% of lactone **24**, 44% of acetoxymethyl nitro ester **25a** and 17% of ethyl 2-formyl-1-cyclopentene-carboxylate (**29**).[37] The analogous oxidation of **22b** yields 51 and 5% of two of the four possible stereoisomers of **25b** and 15% of **29**. The acetoxy methyl group of **25a** is probably *trans* to the carboxylate, because hydrolysis of the acetate and heating the hydroxy ester with acid does not form lactone **24**. The stereochemistry of the **25b** could not be assigned.

Reaction of **22** with $Mn(OAc)_3$ will form the enolate which will cyclize to radical **23**.[17] Oxidation and cyclization will give lactone **24**, while oxidation and reaction with solvent will give acetate **25**. These reactions are analogous to those observed with diethyl 4-pentenylmalonate.[38] A possible mechanism for the formation of aldehyde **29** starts with cyclization of radical **23** onto the nitro group to give bicyclic radical **26**, which can fragment to give nitroso alkoxy radical **27**. Oxidation of **27**, R=H, or fragmentation with loss of Et˙ from **27**, R=Et, will give nitroso aldehyde **28**. Oxidation of the nitroso group to a nitro group and elimination of nitrite will give **29** (Scheme 6).

If this scheme is correct, decreasing the $Cu(OAc)_2$ concentration in the oxidation of **22a** should decrease the yield of **24** and **25a** and increase the yield of aldehyde **29**. On decreasing from 1.0 equiv. of $Cu(OAc)_2$ to 0.1 and then to 0 equiv., the yield of **24** decreased from 17 to 16 and 14%, respectively, the yield of **25a** decreased from 44 to 30 and



Scheme 6.

21%, respectively, and the yield of **29** increased from 17 to 33 and 43%, respectively. These results suggest that rearrangement of radical **23** before oxidation leads to aldehyde **29**.

In conclusion, our results indicate that reaction of α-unsubstituted nitroacetates with $Mn(OAc)_3$ gives mixtures of isoxazolines, formed by dehydration to a nitrile oxide that undergoes cycloaddition, and isoxazoline oxides or cyclopropane, formed by oxidative cyclization. Oxidative cyclization is favored with electron-rich alkenes and cycloaddition with the nitrile oxide to give isoxazolines is favored with electron-poor alkenes. This analysis clearly explains the results obtained by Chuang and Strekhan. On the other hand, α-substituted nitroacetates cannot undergo dehydration to give nitrile oxides and undergo only radical reactions.

3. Experimental

3.1. General

NMR spectra were recorded at 400 MHz in $CDCl_3$. Chemical shifts are reported in δ (ppm) and coupling constants in Hz. IR spectra are reported in cm^{-1}.

3.1.1. Allyl nitroacetate (3a). A solution of allyl alcohol (73 mg, 1.26 mmol) in 3 mL of THF was added to a solution of DCC (389 mg, 1.89 mmol) and nitroacetic acid[9] (132 mg, 1.26 mmol) in 3 mL of THF at 0°C under nitrogen. The resulting mixture was stirred at 0 to 25°C for 20 h. The mixture was filtered to remove DCU and extracted with CH_2Cl_2 (4×5 mL). The combined extracts were dried over Na_2SO_4 and concentrated. Flash chromatography on silica gel (7:1 hexane/EtOAc) gave 122 mg (67%) of **3a**[10] as a colorless liquid: ^{1}H NMR 5.93 (ddt, 1, *J*=17.7, 10.4, 6.1 Hz), 5.39 (dd, 1, *J*=1.2, 17.7 Hz), 5.33 (br d, 1, *J*=10.4 Hz), 5.20 (s, 2), 4.76 (d, 2, *J*=6.1 Hz); ^{13}C NMR 161.5, 130.3, 120.0, 76.1, 67.4; IR (neat) 3037, 1756, 1567, 1335, 1207.

3.1.2. Cyclization of allyl nitroacetate (3a). Allyl nitroacetate (**3a**) (40 mg, 0.276 mmol) was added to a solution of $Mn(OAc)_3{\cdot}2H_2O$ (148 mg, 0.552 mmol), $Cu(OAc)_2{\cdot}H_2O$ (55.1 mg, 0.276 mmol) and NaOAc (45.2 mg, 0.552 mmol) in 2 mL of acetic acid at 25°C under nitrogen. The resulting mixture was stirred at 90°C for 45 min, at which time the brown solution became blue. The reaction mixture was cooled, diluted with water (5 mL) and extracted with CH_2Cl_2 (3×5 mL). The combined extracts were washed successively with water and saturated $NaHCO_3$, dried over Na_2SO_4, and concentrated. Flash chromatography on silica gel (20:1 to 5:1 hexane/EtOAc) gave 8 mg (20%) of recovered **3**, followed by 1.2 mg (3, 4% based on recovered **3a**) of 1-nitro-3-oxa-bicyclo[3.1.0]-hexan-2-one (**2a**) as a colorless liquid, 3.3 mg (10%) of a 1:1 mixture of **2a** and 3a,4-dihydro-3*H*,6*H*-furo[3,4-*c*]isoxazol-6-one (**7**), and 11.6 mg (33%) of pure **7** as a white solid. The calculated yields are 7% (9% based on recovered **3a**) of **2a** and 38% (48% based on recovered starting material) of **7**.

Data for cyclopropane ***2a***. ^{1}H NMR 4.53 (dd, 1, *J*=4.9, 10.2 Hz), 4.22 (br d, 1, *J*=10.2 Hz), 3.24 (ddd, 1, *J*=9.2, 6.1, 4.9 Hz), 2.78 (dd, 1, *J*=6.1, 9.2 Hz), 1.74 (dd, 1, *J*=6.1, 6.1 Hz); ^{13}C NMR 66.7, 30.0, 22.1 (two quaternary carbons were not observed); IR (neat) 3105, 1788, 1547, 1376, 1262, 1106; HRMS (CI) calcd for $C_5H_6NO_4^+$ (MH^+) 144.0297, found 144.0301.

Data for isoxazoline ***7***. Mp 81–82°C (lit.[15] mp 82°C); ^{1}H NMR 4.99–4.94 (m, 1), 4.80–4.76 (m, 1), 4.45–4.28 (m, 3); ^{13}C NMR 158.0, 156.5, 78.1, 70.4, 49.0; IR (neat), 1778, 1630, 1368, 1083; HRMS (CI) calcd for $C_5H_6NO_3^+$ (MH^+) 128.0348, found 128.0346. The spectral data are identical to those reported previously.[15]

3.1.3. Preparation of *cis*-2-penten-1-yl nitroacetate (9a). *cis*-2-Penten-1-yl nitroacetate (**9a**) was prepared analogously to **3** from *cis*-2-penten-1-ol (172 mg, 2.0 mmol), nitroacetic acid (210 mg, 2.0 mmol) and DCC (618 mg, 3.0 mmol) in 6 mL of THF. Normal workup and flash chromatography on silica gel (10:1 hexane/EtOAc) gave 215 mg (62%) of **9a** as a colorless liquid: ^{1}H NMR 5.74 (dt, 1, *J*=11.2, 7.2 Hz), 5.50 (dt, 1, *J*=11.2, 6.7 Hz), 5.17 (s, 2), 4.70 (d, 2, *J*=6.7 Hz), 2.14 (dq, 2, *J*=7.2, 7.2 Hz), 1.01 (t, 3, *J*=7.2 Hz); ^{13}C NMR 161.7, 139.1, 120.7, 76.3, 62.6, 20.9, 13.9; IR (neat) 3034, 1754, 1567, 1332, 1204.

3.1.4. Preparation of *trans*-2-penten-1-yl nitroacetate (9b). *trans*-2-Penten-1-yl nitroacetate (**9b**) was prepared analogously to **3** from *trans*-2-penten-1-ol (172 mg, 2.0 mmol), nitroacetic acid (210 mg, 2.0 mmol) and DCC (618 mg, 3.0 mmol) in 6 mL of THF. Normal workup and flash chromatography on silica gel (10:1 hexane/EtOAc) gave 243 mg (70%) of **9b** as a colorless liquid: ^{1}H NMR 5.90 (dt, 1, *J*=15.3, 7.2 Hz), 5.56 (dt, 1 *J*=15.3, 6.7 Hz), 5.18 (s, 2), 4.70 (d, 2, *J*=6.7 Hz), 2.10 (dq, 2, *J*=7.2, 7.2 Hz), 1.01 (t, 3, *J*=7.2 Hz); ^{13}C NMR 161.6, 140.4, 121.0, 76.3, 67.9, 25.2, 12.9; IR (neat) 3034, 1754, 1566, 1336, 1202.

3.1.5. Cyclization of *cis*-2-penten-1-yl nitroacetate (9a). A solution of **9a** (40 mg, 0.231 mmol), $Mn(OAc)_3{\cdot}2H_2O$ (124 mg, 0.462 mmol), $Cu(OAc)_2{\cdot}H_2O$ (46.1 mg, 0.231 mmol) and NaOAc (37.8 mg, 0.462 mmol) in 2 mL of acetic acid was stirred at 90°C under nitrogen for 60 min. Normal workup and flash chromatography on silica (20:1 to 5:1 hexane/EtOAc) gave 7.2 mg (18%) of recovered **9a**, followed by 14.4 mg (40, 49% based on recovered starting material) of (3α,3aβ)-3a,4-dihydro-3-ethyl-3*H*,6*H*-furo[3,4-*c*]isoxazol-6-one (**10a**) as a colorless liquid: ^{1}H NMR 4.98 (ddd, 1, *J*=6.1, 9.0, 11.1 Hz), 4.63 (dd, 1, *J*=7.3, 8.3 Hz), 4.47 (ddd, 1, *J*=10.5, 9.0, 7.3 Hz), 4.41 (dd, 1, *J*=10.5, 8.3 Hz), 1.83 (ddq, 1, *J*=13.9, 6.1, 7.3 Hz), 1.53 (ddq, 1, *J*=13.9, 11.1, 7.3 Hz), 1.00 (t, 3, *J*=7.3 Hz); ^{13}C NMR 158.3, 154.7, 89.7, 65.9, 50.5, 23.2, 9.9; IR (neat) 1783, 1632, 1368, 1271, 1077; HRMS (CI) calcd for $C_7H_{10}NO_3^+$ (MH^+) 156.0661, found 156.0666.

3.1.6. Cyclization of *trans*-2-penten-1-yl nitroacetate (9b). A solution of **9b** (40 mg, 0.231 mmol), $Mn(OAc)_3{\cdot}2H_2O$ (124 mg, 0.462 mmol), $Cu(OAc)_2{\cdot}H_2O$ (46.1 mg, 0.231 mmol) and NaOAc (37.8 mg, 0.462 mmol) in 2 mL

of acetic acid was stirred at 90°C under nitrogen for 50 min. Normal workup and flash chromatography on silica gel (20:1 to 5:1 hexane/EtOAc) gave 12.9 mg (32%) of recovered **9b**, followed by 14.4 mg (39, 60% based on recovered starting material) of (3α,3aα)-3a,4-dihydro-3-ethyl-3*H*,6*H*-furo[3,4-*c*]isoxazol-6-one (**10b**) as a colorless liquid: ^{1}H NMR 4.74 (ddd, 1, *J*=12.2, 6.7, 6.7 Hz), 4.71 (dd, 1, *J*=9.1, 8.9 Hz), 4.29 (dd, 1, *J*=8.9, 8.7 Hz), 3.94 (ddd, 1, *J*=12.2, 9.1, 8.7 Hz), 2.13–2.02 (m, 1), 1.98–1.87 (m, 1), 1.04 (t, 3, *J*=7.3 Hz); ^{13}C NMR 158.4, 157.1, 94.6, 69.9, 52.2, 25.7, 10.1; IR (neat) 2972, 1785, 1623, 1364, 1288, 1072.

3.1.7. Cyclization of ethyl nitroacetate with ethyl acrylate (16a). Ethyl nitroacetate (**12**) (34.1 mg, 0.25 mmol) was added to a solution of $Mn(OAc)_3{\cdot}2H_2O$ (135.4 mg, 0.50 mmol) and ethyl acrylate (**16a**) (50 mg, 0.50 mmol) in 10 mL of acetic acid at 25°C under nitrogen. The resulting mixture was stirred at 90°C for 30 min at which time the brown color of Mn(III) disappeared. The reaction mixture was cooled, diluted with water (10 mL) and extracted with CH_2Cl_2 (3×10 mL). The combined organic extracts were washed successively with water and saturated $NaHCO_3$, dried over Na_2SO_4 and concentrated. Flash chromatography on silica gel (10:1 hexane/EtOAc) gave 17.1 mg (50%) of recovered **12** followed by 12.8 mg (24, 47% based on recovered **12**) of diethyl 4,5-dihydro-3,5-isoxazoledicarboxylate (**19a**) as a colorless liquid: ^{1}H NMR 5.19 (dd, 1, *J*=11.6, 8.0 Hz), 4.37 (q, 2, *J*=7.3 Hz), 4.27 (q, 2, *J*=7.3 Hz), 3.53 (dd, 1, *J*=18.3, 8.0 Hz), 3.48 (dd, 1, *J*=18.3, 11.6 Hz), 1.38 (t, 3, *J*=7.3 Hz), 1.32 (t, 3, *J*=7.3 Hz); ^{13}C NMR 168.9, 159.8, 151.0, 79.8, 62.4, 62.3, 37.5, 14.1 (2C); IR (neat) 2987, 1741, 1730, 1377, 1255, 1210. The spectral data are identical to those previously reported.[23,25]

3.1.8. Cyclization of ethyl nitroacetate with styrene (16b). A solution of ethyl nitroacetate (**12**) (34.1 mg, 0.25 mmol), styrene (**16b**) (26 mg, 0.25 mmol), and $Mn(OAc)_3{\cdot}2H_2O$ (135.4 mg, 0.50 mmol) in 10 mL of acetic acid was stirred at 90°C under nitrogen for 1.5 h. Normal workup and flash chromatography on silica gel (50:1 to10:1 hexane/EtOAc) gave 20.3 mg (60%) of recovered **12** and 1.8 mg (4, 10% based on recovered **12**) of ethyl 4,5-dihydro-5-phenyl-3-isoxazolecarboxylate 2-oxide (**20b**) as a colorless liquid: ^{1}H NMR 7.48–7.41 (m, 5), 5.72 (dd, 1, *J*=9.8, 8.0 Hz), 4.33 (q, 2, *J*=7.3 Hz), 3.82 (dd, 1, *J*=17.1, 9.8 Hz), 3.44 (dd, 1, *J*=17.1, 8.0 Hz), 1.34 (t, 3, *J*=7.3 Hz); IR (neat) 1733, 1690 (shoulder), 1620, 1557, 1370, 1242, 1021. The spectral data are identical to those previously reported.[30]

3.1.9. Cyclization of ethyl nitroacetate with 1-hexene (16c). A solution of ethyl nitroacetate (**12**) (34.1 mg, 0.25 mmol), 1-hexene (**16c**) (42.0 mg, 0.50 mmol), and $Mn(OAc)_3{\cdot}2H_2O$ (134.1 mg, 0.50 mmol) in 4 mL of acetic acid was stirred at 90°C for 90 min in a sealed tube. Normal workup and flash chromatography on silica gel (20:1 hexane/EtOAc) gave 10.0 mg (20, 25% based on recovered starting material) of ethyl 5-butyl-4,5-dihydro-3-isoxazolecarboxylate (**19c**) as a colorless liquid, followed by 7.2 mg (21%) of recovered **12**, and 27.4 mg (51, 65% based on recovered starting material) of ethyl 5-butyl-4,5-dihydro-3-isoxazolecarboxylate 2-oxide (**20c**) as a colorless liquid.

*Data for **19c***. ^{1}H NMR 4.84–4.76 (m, 1), 4.34 (q, 2, *J*=7.3 Hz), 3.25 (dd, 1, *J*=17.7, 11.0 Hz), 2.84 (dd, 1, *J*=17.7, 8.5 Hz), 1.82–1.73 (m, 1), 1.64–1.56 (m, 1), 1.46–1.26 (m, 7), 0.92 (br t, 3, *J*=7.3 Hz); ^{13}C NMR 160.9, 151.3, 84.2, 62.0, 38.3, 34.7, 27.2, 22.4, 14.1, 13.9; IR (neat) 1719, 1587, 1379, 1257, 1126; HRMS (DEI) calcd for $C_{10}H_{18}NO_3^+$ (MH^+) 200.1287, found 200.1284.

*Data for **20c***. ^{1}H NMR 4.75–4.67 (m, 1), 4.33 (q, 2, *J*=7.2 Hz), 3.44 (dd, 1, *J*=16.5, 9.1 Hz), 3.05 (dd, 1, *J*=16.5, 7.5 Hz), 1.90–1.80 (m, 1), 1.73–1.64 (m, 1), 1.50–1.28 (m, 7), 0.92 (br t, 3, *J*=7.3 Hz); ^{13}C NMR 159.2, 108.5, 76.3, 61.7, 35.8, 34.4, 26.8, 22.3, 14.2, 13.8; IR (neat) 1734, 1616, 1382, 1244, 1027; HRMS (DEI) calcd for $C_{10}H_{18}NO_4^+$ (MH^+) 216.1236, found 216.1231.

3.1.10. Preparation of ethyl 2-nitro-6-heptenoate (22a). 5-Iodo-1-pentene (**21a**) (196 mg, 1.0 mmol) was added to a solution of ethyl nitroacetate (**12**) (133 mg, 1.0 mmol) in 2 mL of DMF containing tetraethylammonium chloride (3.2 mg, 20 μmol) and anhydrous $KHCO_3$ (100 mg, 1.0 mmol) at room temperature under nitrogen.[36] The reaction mixture was stirred at 70°C for 20 h. DMF was removed under vacuum, and the residue was diluted with water and extracted with CH_2Cl_2 (4×5 mL). The combined extracts were dried over $MgSO_4$ and concentrated. Flash chromatography on silica gel (40:1 to 10:1 hexane/Et_2O) gave 96 mg (48, 62% based on recovered starting material) of **22a** as a colorless liquid, followed by 31 mg (23%) of recovered **12**.

*Data for **22a***. ^{1}H NMR 5.76 (ddt, 1, *J*=17.1, 10.4, 6.7 Hz), 5.11 (dd, 1, *J*=5.5, 9.8 Hz), 5.05 (dd, 1, *J*=17.1, 1.2 Hz), 5.02 (dd, 1, *J*=10.4, 1.2 Hz), 4.29 (q, 2, *J*=7.0 Hz), 2.24–2.34 (m, 1), 2.10–2.19 (m, 3), 1.53–1.46 (m, 2), 1.30 (t, 3, *J*=7.0 Hz); ^{13}C NMR 164.5, 137.0, 115.9, 88.0, 63.0, 32.7, 29.6, 24.7, 13.9; IR (neat) 1749, 1558, 1372, 1186.

3.1.11. Preparation of ethyl 2-nitro-*cis*-6-nonenoate (22b). Ethyl 2-nitro-*cis*-6-nonenoate (**22b**) was prepared analogously to **22a** from *cis*-7-iodo-3-heptene (**21b**) (224 mg, 1.0 mmol), ethyl nitroacetate (**12**) (133 mg, 1.0 mmol) and $KHCO_3$ (100 mg, 1.0 mmol) in 2 mL of DMF in the presence of tetraethyl ammonium chloride (3.2 mg, 20 μmol). Normal workup and flash chromatography on silica gel (50:1 to 10:1 hexane/EtOAc) gave 11 mg of recovered **21a**, 86.7 mg (38, 53% based on recovered **12**) of **22b** as a colorless liquid, followed by 38 mg (29%) of recovered **12**:

*Data for **22b***. ^{1}H NMR 5.47–5.40 (m, 1), 5.30–5.24 (m, 1), 5.09 (dd, 1, *J*=5.5, 9.1 Hz), 4.29 (q, 2, *J*=7.3 Hz), 2.33–2.23 (m, 1), 2.19–1.98 (m, 5), 1.49–1.41 (m, 2), 1.31 (t, 3, *J*=7.3 Hz), 0.96 (t, 3, *J*=7.3 Hz); ^{13}C NMR 164.5, 133.2, 127.1, 88.1, 62.9, 29.7, 26.1, 25.5, 20.5, 14.2, 13.9; IR (neat) 3007, 1750, 1558, 1373.

3.1.12. Oxidative cyclization of ethyl 2-nitro-6-heptenoate (22a). Nitroheptenoate **22a** (30 mg, 0.15 mmol) was added to a solution of $Mn(OAc)_3{\cdot}2H_2O$ (81 mg, 0.30 mmol, 2 equiv.), $Cu(OAc)_2{\cdot}H_2O$ (30 mg, 0.15 mmol, 1 equiv.) and NaOAc (24.6 mg, 0.30 mmol, 2 equiv.) in 2 mL of acetic acid at 25°C under nitrogen. The resulting mixture was

stirred and heated to 90°C for 55 min at which time the brown color of Mn(III) became blue. The reaction mixture was cooled, diluted with water (5 mL) and extracted with CH_2Cl_2 (3×5 mL). The combined extracts were washed successively with water twice and saturated $NaHCO_3$, dried over Na_2SO_4 and concentrated. Flash chromatography on silica gel (30:1 to 5:1 hexanes/EtOAc) gave 4.3 mg (17%) of ethyl 2-formyl-1-cyclopentene-1-carboxylate (**29**), followed by 17.2 mg (44%) of ethyl (1*R**,2*S**)-2-acetyloxymethyl-1-nitro-cyclopentanecarboxylate (**25a**), and 4.6 mg (18%) of *cis*-6a-nitrohexahydro-1*H*-cyclopenta[*c*]furan-1one (**24**).

Data for ***24***. ^{1}H NMR 4.75 (dd, 1, *J*=9.8, 7.9 Hz), 4.17 (dd, 1, *J*=9.8, 2.5 Hz), 3.45–3.39 (m, 1), 2.83 (ddd, 1, *J*=14.0, 7.8, 7.8 Hz), 2.47 (ddd, 1, *J*=14.0, 5.8, 5.8 Hz), 2.31–2.24 (m, 1), 2.06–1.95 (m, 1), 1.85–1.70 (m, 2); ^{13}C NMR 72.6, 47.4, 34.6, 33.4, 25.2 (two quaternary carbons were not observed); IR (neat) 1785, 1557, 1350; HRMS (CI) calcd for $C_7H_{10}NO_4^+$ (MH^+) 172.0615, found 172.0621.

Data for ***25a***. ^{1}H NMR 4.36–4.23 (m, 2), 4.25 (dd, 1, *J*=11.6, 5.5 Hz), 4.15 (dd, 1, *J*=11.6, 6.7 Hz), 3.10–3.01 (m, 1), 2.84 (ddd, 1, *J*=14.4, 8.5, 6.1 Hz), 2.26 (ddd, 1, *J*=14.4, 9.8, 6.1 Hz), 2.13–1.98 (m, 2), 2.03 (s, 3), 1.86–1.59 (m, 2), 1.30 (t, 3, *J*=7.0 Hz); ^{13}C NMR 170.6, 166.6, 99.5, 63.1, 62.9, 46.4, 35.9, 27.4, 21.6, 20.6, 13.7; IR (neat) 1746, 1550, 1369; HRMS (CI) calcd for $C_{11}H_{18}NO_6^+$ (MH^+) 260.1134, found 260.1124.

Data for ***29***.[37] ^{1}H NMR 10.50 (s, 1), 4.31 (q, 2, *J*=7.3 Hz), 2.87 (dddd, 2, *J*=7.6, 7.6, 2.8, 2.8 Hz), 2.72 (dddd, 2, *J*=7.6, 7.6, 2.8, 2.8 Hz), 1.93 (dddd, 2, *J*=7.6, 7.6, 7.6, 7.6 Hz), 1.35 (t, 3, *J*=7.3 Hz); ^{13}C NMR 190.8, 164.1, 150.3, 146.8, 61.3, 35.5, 31.6, 21.0, 14.2; IR (neat) 1777, 1709, 1675; HRMS (CI) calcd for $C_9H_{13}NO_3^+$ (MH^+) 169.0857, found 169.0865.

3.1.13. Oxidative cyclization of ethyl 2-nitro-*cis*-6-nonenoate (22b). A solution of **22b** (40 mg, 0.175 mmol), $Mn(OAc)_3{\cdot}2H_2O$ (94 mg, 0.35 mmol), $Cu(OAc)_2{\cdot}H_2O$ (35 mg, 0.175 mmol) and NaOAc (28.7 mg, 0.35 mmol) in 2 mL of acetic acid was stirred at 90°C under nitrogen for 60 min. Normal workup and flash chromatography on silica gel (10:1 to 5:1 hexane/EtOAc) gave 23.4 mg (48%) of a major isomer of ethyl 2-[1-(acetyloxy)-ethyl]-1-nitro-cyclopentanecarboxylate (**25b**) as a colorless liquid, 4.0 mg (8%) of a 3:5 mixture of the major and minor isomers of **25b**, and 4.4 mg (15%) of **29** as a colorless liquid. The calculated yields of the major isomer and minor isomer of **25b** are 51 and 5%, respectively.

Data for ***25b*** *major isomer*. ^{1}H NMR 5.11–5.07 (m, 1), 4.33–4.20 (m, 2), 2.99–2.93 (m, 1), 2.86–2.78 (m, 1), 2.17–2.06 (m, 2), 2.02–1.95 (m, 2), 1.95 (s, 3), 1.78–1.69 (m, 2), 1.60–1.49 (m, 2), 1.28 (t, 3, *J*=7.3 Hz), 0.95 (t, 3, *J*=7.3 Hz); ^{13}C NMR 170.3, 166.9, 98.9, 72.5, 62.7, 49.0, 35.9, 26.8, 23.6, 21.6, 20.5, 13.7, 9.9; IR (neat) 2972, 1747, 1551, 1371, 1238; HRMS (CI) calcd for $C_{13}H_{25}N_2O_6^+$ (MNH_4^+) 305.1713, found 305.1719.

Partial data for ***25b*** *minor isomer*. ^{1}H NMR 4.98–4.94 (m, 1), 4.32–4.24 (m, 2), 3.16–3.09 (m, 1), 2.91–2.84 (m, 1), 2.31–2.23 (m, 2), 2.08–1.72 (m, 4), 1.98 (s, 3), 1.60–1.46 (m, 2), 1.31 (t, 3, *J*=7.3 Hz), 0.90 (t, 3, *J*=7.3 Hz).

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