Termination of Mn(III)-Based Oxidative Free-Radical Cyclizations by Addition to Nitriles. Formation of Cyclopentanones and Cyclohexanones

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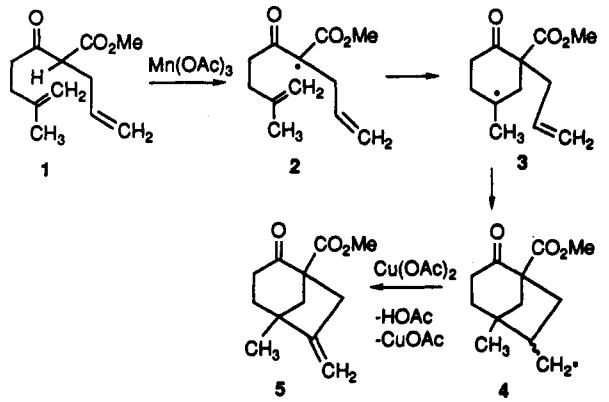
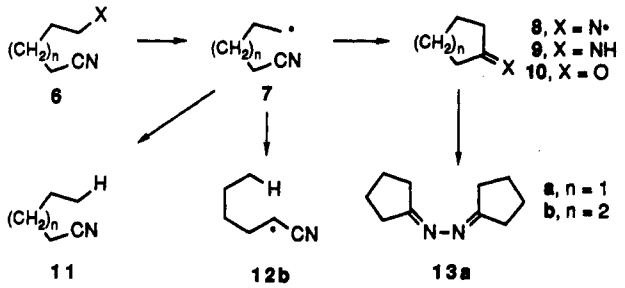
Mn(III)-based oxidative free-radical tandem cyclizations and annulations can be terminated by addition to nitriles. Cyclopentanones **20a** (51%), **24a** (57%), and **32a** (54%) are formed in good yield. Annulation to give cyclohexanone **32b** (41%) proceeds in moderate yield, although **20b** (8%) and **24b** (13%) are formed in poor yield in tandem cyclizations. Pyridine **39** (15%) is formed in ethanol by condensation of the enamine tautomer **37** of imine **31a** with the oxidation byproduct **33a** produced from radical **29a**.

Introduction

We recently reported that oxidative tandem cyclization[1] of **1** with $Mn(OAc)_3 \cdot 2H_2O$ and $Cu(OAc)_2 \cdot H_2O$ provides bicyclo[3.2.1]octane **5** in 86% yield.[1b] Oxidation of acetoacetate **1** with Mn(III) gives radical **2** which undergoes two sequential cyclizations to give primary radical **4**. Oxidation of **4** with Cu(II) affords alkene **5**. Replacement of the allyl group of **1** with other radical acceptors might provide a route to bicycloalkanes containing different functionality.



The cyclization of δ-cyano radicals, as shown for the parent **7a**, is a general route to cyclopentanones.[2] These reactions are typically carried out by reduction of the halide or thiocarbonyl imidazolide **6a** with *n*-Bu_3SnH to give **7a**.[2a-c] Cyclization of **7a** affords the iminyl radical **8a** which is reduced by *n*-Bu_3SnH to afford the imine **9a**; hydrolysis affords the cyclopentanone **10a**. Since the cyclization of δ-cyano radicals is slower than the cyclization of 5-hexenyl radicals, reduction of **7a** by *n*-Bu_3SnH to give **11a** is often a serious side reaction.[2c,f,g] Azine **13a** may be obtained if radicals of type **7a** are generated in the absence of a hydrogen donor by treatment of **6a** with hexamethyldibutylstannane.[2c] The cyclization of ε-cyano radicals **7b** to give cyclohexanones rarely proceeds in acceptable yield.[2c,e,h,3] Reduction of **7b** by *n*-Bu_3SnH to give **11b** or 1,5-hydrogen shift to give α-cyano radical **12b** are usually the major reactions.



Results and Discussion

We now report that Mn(III)-based oxidative free-radical tandem cyclizations can be terminated by addition to nitriles. Acetoacetates **15a** and **15b** are readily available by reaction of the sodium salt of **14**[4] with bromoacetonitrile[5] and acrylonitrile[6] in 65% and 24% yield, respectively. Oxidative cyclization of **15a** with 2 equiv of $Mn(OAc)_3 \cdot 2H_2O$ in ethanol for 24 h affords 51% of **20a**. The starting material is completely consumed; the remaining material in these reactions is uncharacterizable oligomer. As in the conversion of **1** to **5**, oxidation of **15a** gives radical **16a** which cyclizes to afford the tertiary δ-cyano radical **17a**. This radical cyclizes to iminyl radical **18a** which either abstracts a hydrogen atom from the solvent or another molecule of **15a** to give **19a** or is reduced and protonated to give imine **19a**. Hydrolysis of the imine gives ketone **20a**.

The source of the hydrogen atom for the reduction of iminyl radical **8a** to imine **9a** is obvious if the cyclization is carried out in the presence of *n*-Bu_3SnH. The source of the hydrogen in the reduction of iminyl radical **18a** to imine **19a** is less obvious. We demonstrated that ethanol reduces primary and alkenyl radicals generated in Mn(III)-based oxidative free-radical cyclizations suggesting that ethanol might be the hydrogen source for the reduction of **18a**.[1e] Acetic acid is less effective in reducing primary and alkenyl radicals. Oxidative cyclization of **15a** with two equiv of $Mn(OAc)_3 \cdot 2H_2O$ in acetic acid affords 33% of **20a**, indicating that ethanol is not needed as a hydrogen donor and suggesting that solvent is not involved in the reduction of the iminyl radical to the imine.

(1) (a) Snider, B. B.; Buckman, B. O. *Tetrahedron* **1989**, *45*, 6969. (b) Dombroski, M. A.; Kates, S. A.; Snider, B. B. *J. Am. Chem. Soc.* **1990**, *112*, 2759. (c) Kates, S. A.; Dombroski, M. A.; Snider, B. B. *J. Org. Chem.* **1990**, *55*, 2427. (d) Curran, D. P.; Morgan, T. M.; Schwartz, C. E.; Snider, B. B.; Dombroski, M. A. *J. Am. Chem. Soc.* **1991**, *113*, 6607. (e) Snider, B. B.; Merritt, J. E.; Dombroski, M. A.; Buckman, B. O. *J. Org. Chem.* **1991**, *56*, 5544.

(2) (a) Clive, D. L. J.; Beaulieu, P. L.; Set, L. *J. Org. Chem.* **1984**, *49*, 1313 and references cited therein. (b) Chenera, B.; Chuang, C.-P.; Hart, D. J.; Hsu, L.-Y. *J. Org. Chem.* **1985**, *50*, 5409 and references cited therein. (c) Tsang, R.; Fraser-Reid, B. *J. Am. Chem. Soc.* **1986**, *108*, 2116. (d) Beckwith, A. L. J.; O'Shea, D. M.; Westwood, S. W. *J. Am. Chem. Soc.* **1988**, *110*, 2565. (e) Yeung, B.-W.; Contelles, J. L. M.; Fraser-Reid, B. *J. Chem. Soc., Chem. Commun.* **1989**, 1160. (f) Kilburn, J. D. *Tetrahedron Lett.* **1990**, *31*, 2193. (g) Esch, P. M.; Hiemstra, H.; Speckamp, W. N. *Tetrahedron Lett.* **1990**, *31*, 759. (h) Knapp, S.; Gibson, F. S.; Choe, Y. H. *Tetrahedron Lett.* **1990**, *31*, 5397.

(3) See footnote 12 in ref 2b.

(4) Hirama, M.; Shimizu, M.; Iwashita, M. *J. Chem. Soc., Chem. Commun.* **1983**, 599.

(5) Cummings, W. A. W.; Davis, A. C. *J. Chem. Soc.* **1964**, 4591.

(6) Albertson, N. F. *J. Am. Chem. Soc.* **1950**, *72*, 2594.

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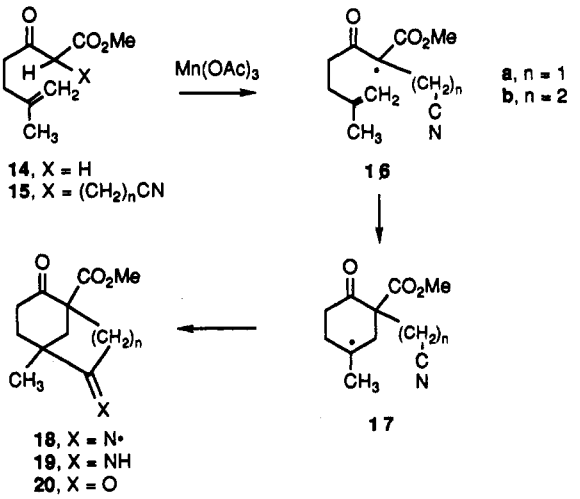
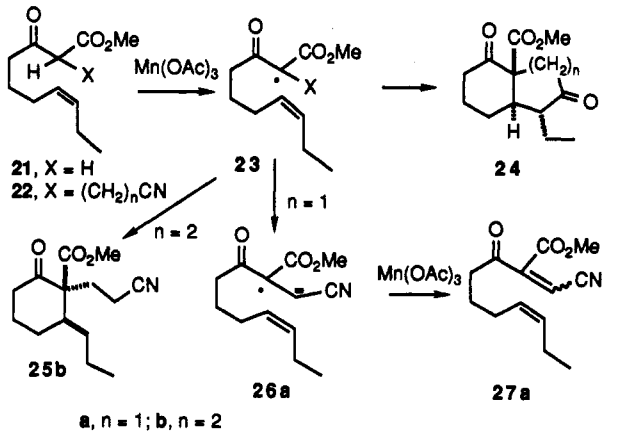


Alternatively, the α-hydrogen of acetoacetate **15a** could be transferred to iminyl radical **18a** to give imine **19a** and radical **16a** in a free-radical chain reaction. If the α-hydrogen of **15a** is transferred to **18a**, only a catalytic amount of Mn(III) will be required since radical **16a** is generated in the reduction of **18a** to **19a**. Reaction of **15a** with only 0.5 equiv of $Mn(OAc)_3 \cdot 2H_2O$ in either acetic acid or ethanol results in the complete consumption of **15a** and the formation of 30–50% of **20a** indicating that the reaction is catalytic in Mn(III). Chain reactions involving hydrogen transfer are well-known and usually very short.[7] Complete consumption of **15a** with 0.5 equiv of $Mn(OAc)_3 \cdot 2H_2O$ requires only that the chain length be greater than 2. Two equiv of $Mn(OAc)_3 \cdot 2H_2O$ were still used in most reactions. $Cu(OAc)_2 \cdot H_2O$ is not required as a cooxidant, although its use does not have a deleterious effect.

The reaction could also be terminated by a third pathway which is not available to carbon-centered radicals. Protonation of iminyl radical **18a** to give the iminium radical and reduction of the iminium radical by Mn(II) would give imine **19a**. There is limited precedent for the reduction of nitrogen-centered radicals. The reduction of aminium radicals by Fe(II) has been proposed as a termination step in a chain process.[8] Although Mn(II) is not usually considered to be a reducing agent, Mn(II) reduces alkyl hydroperoxides to hydroxide ion and an alkoxy radical.[9] The Mn(II) necessary for the reduction of **18a** is generated in the formation of **16a**. We examined the effect of added Mn(II) on the reaction with the expectation that the yield of products might be improved if this termination procedure were operative. Addition of 1.0 equiv of $Mn(OAc)_2 \cdot 4H_2O$ to the oxidative cyclization of **15a** and **22a** and the annulation of **28b** and methylenecyclopentane had no effect on the yield of products. However, addition of 1.0 equiv of $Mn(OAc)_2 \cdot 4H_2O$ to the annulation of **28a** and methylenecyclopentane doubled the yield of **32a** (vide infra), indicating that this termination procedure might be operative.

Oxidative cyclization of **15b** provides only 8% of bicyclo[3.3.1]nonanedione **20b**. Presumably, oxidation and cyclization to give tertiary radical **17b** occur normally. Cyclization of ϵ-cyano radical **17b** to give iminyl radical **18b** should be much slower than cyclization of δ-cyano radical **17a** permitting undesired side reactions to predominate.

This reaction can also be used for the synthesis of indanediones and decalindiones. Acetoacetates **22a** and **22b** are readily available by reaction of the sodium salt of **21**[1c,d] with bromoacetonitrile[5] and acrylonitrile[6] in 56% and 20% yield, respectively. Oxidative cyclization of **22a** with 2 equiv of $Mn(OAc)_3 \cdot 2H_2O$ in acetic acid affords 40% of **24a**. The stereochemistry of **24** was assigned by analogy to the oxidative cyclization of the substrate with an α-allyl substituent.[1b,d] To our surprise, cyclization does not occur when ethanol is used as solvent; only recovered **22a** and polymer are isolated. Although we previously observed significant solvent effects in related oxidative cyclizations,[1e] we did not anticipate that the cyclization of radical **23a** would be significantly slower in ethanol than in acetic acid. Therefore, we considered the possibility that side reactions of **23a** would be faster in ethanol than in acetic acid.



The presence of the radical should significantly enhance the acidity of the proton adjacent to the cyano group.[10] Deprotonation of **23a** should give radical anion **26a** which should be oxidized rapidly by Mn(III) to **27a** which should polymerize or react with nucleophiles present in solution. Deprotonation should be much faster in ethanol than in the more acidic solvent, acetic acid. To determine whether the pH of the solution was the crucial factor, we carried out the oxidative cyclization of **22a** in ethanol containing 5 equiv of TFA which affords 57% of bicyclo[3.3.1]nonanedione **24a**. The successful formation of **24a** under these conditions indicates that ethanol is a suitable solvent for the reaction and suggests that deprotonation of **23a** to give radical anion **26a** occurs faster than cyclization to give **24a** in nonacidic solution. Presumably, deprotonation of radical **16a** is not a significant side reaction in ethanol since 6-endo cyclization of **16a** should be much faster than 6-exo cyclization of **23a**.

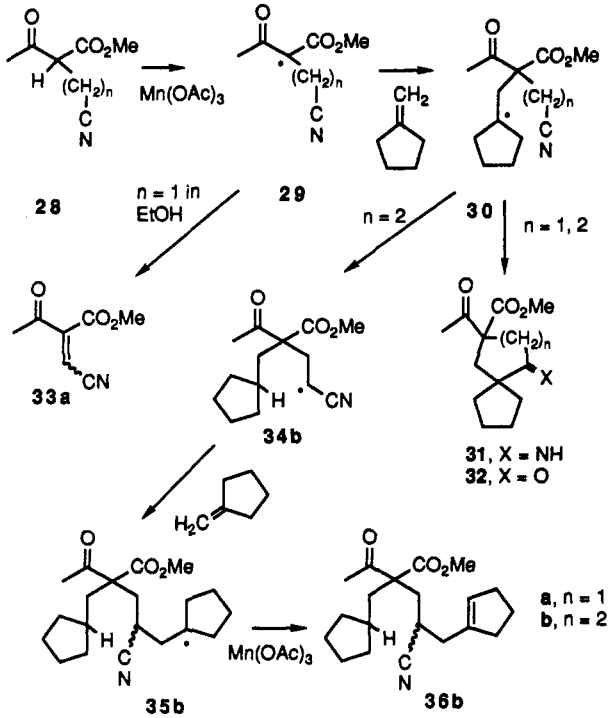
Oxidative cyclization of **22b** in ethanol affords 13% of decalindione **24b** and 4% of cyclohexanone **25b**. Similar results are obtained in acetic acid. The slow cyclization of the monocyclic ϵ-cyano radical is responsible for the low yield of **24b**. Reduction of the monocyclic ϵ-cyano radical,

(7) Giese, B. *Radicals in Organic Synthesis: Formation of Carbon–Carbon Bonds*; Pergamon: Oxford, 1986; Chapter 2.
(8) Minisci, F. *Synthesis* **1973**, 1.
(9) Kochi, J. K. In *Free Radicals*; Kochi, J. K., Ed.; Wiley-Interscience: New York, 1973; Vol. 1, p 639.

(10) Hydroxyalkyl radicals ($R_2C \cdot OH$) are several orders of magnitude more acidic than the corresponding alcohols (R_2CHOH).[11] The radical anion formed by addition of an electron to fumarate or maleate esters is protonated on the carbonyl group to give $(RO)HOC \cdot CH{=}CHCO_2R$ (i), which has a pK_a of 2.8 or 4.8 depending on the stereochemistry of the double bond.[12] Protonation on carbon to give the succinyl radical $RO_2CCH \cdot CH_2CO_2R$ (ii) does not occur. If kinetic effects were not important, these data would indicate that radical ii, which is analogous to **23a**, is less stable than radical i and should therefore be even more acidic than i. It is clear that the pK_a of the methylene group of radicals ii and **23a** should be much less than the value of **23–25** expected for the parent ester and nitrile.
(11) Neta, P. In *Advances in Physical Organic Chemistry*; Gold, V., Bethell, D., Eds.; Academic: London, 1976; Vol. 12, pp 223–297.
(12) Hayon, E.; Simic, M. *Acc. Chem. Res.* **1974**, *7*, 114.

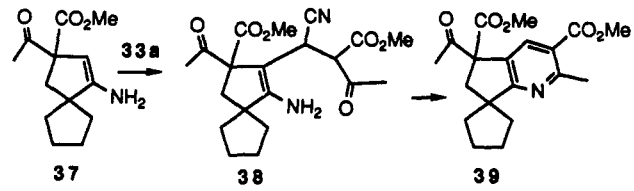
possibly after 1,5-hydrogen shift to give the α-cyano radical, gives **25b**. Deprotonation of **23b** in ethanol is not a significant side reaction since the proton adjacent to the cyano group is separated from the radical by a methylene group.

We previously described Mn(III)-based oxidative free-radical annulations of methyl 2-allylacetoacetate with alkenes.[1a] Analogous annulations can be carried out with methyl (cyanomethyl)acetoacetate (**28a**)[5] and methyl (cyanoethyl)acetoacetate (**28b**).[6] Reaction of **28a** with 2 equiv of $Mn(OAc)_3 \cdot 2H_2O$ and 1 equiv of methylenecyclopentane in ethanol affords 26% of spirocyclopentanone **32a** and 15% of a minor product eventually characterized as pyridine **39**. An absorption at δ 8.24 in the ^1H NMR spectrum and the presence of three carbonyl and five other carbons between δ 100–210 in the ^{13}C NMR spectrum indicated the presence of a pyridine ring;[13] the molecular formula was determined by mass spectroscopy. From this information the structure of **39** could be assigned based on mechanistic considerations.



Oxidation of **28a** should give radical **29a**. Addition of **29a** to methylenecyclopentane should give δ-cyano radical **30a**, which should cyclize to give, after reduction, imine **31a**. Hydrolysis should give ketone **32a**. In ethanol, deprotonation of **29a** to give the radical anion analogous to **26a**, which should be rapidly oxidized to **33a**, is expected to be a significant side reaction. Pyridine **39** can be formed by reaction of imine **31a** with alkene **33a**. Tautomerization of **31a** will give enamine **37**. Michael addition of **37** to **33a** and tautomerization should give enamine **38**. Condensation of the amino group with the ketone and loss of HCN should give pyridine **39**. Pyrones have been formed by analogous condensations and eliminations.[14]

As expected, cyclopentanone **32a** is the sole product from **28a** and methylenecyclopentane in acetic acid (23%) or in ethanol containing TFA (30%). We believe that pyridine **39** is not formed under these conditions since



deprotonation of **29a** to give the radical anion precursor to **33a** is slower in acidic solution as discussed above for the formation of **27a**. It is also possible that more rapid hydrolysis of imine **31a** to ketone **32a** in acidic solution is responsible for the absence of pyridine **39**.

Reaction of **28a** and methylenecyclopentane with 2 equiv of $Mn(OAc)_3 \cdot 2H_2O$ and 1 equiv of $Mn(OAc)_2 \cdot 4H_2O$ gives significantly improved yields of **32a** (54% in ethanol, 47% in acetic acid and 51% in ethanol containing TFA), suggesting that the iminyl radical may be reduced by Mn(II) as discussed above.

Reaction of **28b** with 2 equiv of $Mn(OAc)_3 \cdot 2H_2O$ and 1 equiv of methylenecyclopentane in ethanol affords 41% of spirodecanone **32b** and 21% of the 2:1 adduct **36b**. Addition of radical **29b** to methylenecyclopentane gives ϵ-cyano radical **30b**. Cyclization, reduction, and hydrolysis gives ketone **32b**. Since cyclization of ϵ-cyano radical **30b** is slow, 1,5-hydrogen shift to give the more stable α-cyano radical **34b** can occur. Addition of **34b** to a second molecule of methylenecyclopentane gives tertiary radical **35b** which is oxidized to **36b** by the second equiv of $Mn(OAc)_3 \cdot 2H_2O$.

The structure of **36b** was assigned by examination of the spectral data. The mass spectrum indicates the product is an oxidized 2:1 adduct. An alternative 2:1 product that could be formed by addition of **30b** to methylenecyclopentane followed by oxidation can be excluded since this product would not be a mixture of diastereomers, and since the APT spectra shows the presence of two sp^3 methine carbons while the alternative product has no sp^3 methine carbons. 1,5-Hydrogen shift to give the α-cyano radical **34b** is therefore faster than addition of **30b** to methylenecyclopentane or oxidation of **30b** to the cyclopentene.

These data indicate that Mn(III)-based oxidative free-radical tandem cyclizations and annulations can be terminated by addition to nitriles. Cyclopentanones **20a**, **24a**, and **32a** are formed in good yield. Annulation to give cyclohexanone **32b** proceeds in good yield, although **20b** and **24b** are formed in poor yield. Loss of a proton from the CH_2CN group of radicals **23a** and **29a** in nonacidic solution to give radical anions that are oxidized to alkenes **27a** and **33a**, respectively, appears to be a significant side reaction which is being studied further.

Experimental Section

NMR spectra were determined at 300 MHz in $CDCl_3$. Chemical shifts are reported in δ; coupling constants are reported in Hz. $Mn(OAc)_3 \cdot 2H_2O$ was purchased from Aldrich. Absolute ethanol and glacial acetic acid were used without further purification. Oxidative cyclizations were carried out under nitrogen.

Methyl 2-(Cyanomethyl)-6-methyl-3-oxo-6-heptenoate (15a). To a solution of alcohol-free sodium methoxide (1.47 mmol) in 5 mL of ether was added 14[4] (250 mg, 1.47 mmol) followed by bromoacetonitrile (176 mg, 1.47 mmol).[5] The solution was stirred at 25 °C for 4 h, neutralized with 10% HCl, and extracted with ether. The combined organic layers were dried ($MgSO_4$) and evaporated in vacuo to afford 304 mg (99%) of crude **15a**. Flash chromatography on silica gel (5:1 hexane–EtOAc) gave 200 mg (65%) of **15a** as a clear oil: ^1H NMR 4.76 (br s, 1), 4.66 (br s, 1), 3.92 (t, 1, J = 7.2), 3.82 (s, 3), 2.97 (td, 1, J = 7.6, 18), 2.68 (td, 1, J = 7.6, 18), 2.85 (d, 2, J = 7.2), 2.32 (br t, 2, J = 7.6), 1.74 (br s, 3); ^{13}C NMR 200.5, 166.8, 143.5, 117.3, 110.6, 54.1, 53.3, 40.5, 30.8, 22.5, 15.6; IR (neat) 2960, 2240, 1750, 1720, 1650 cm^{-1}. Anal.

(13) Bouchon, G.; Spohn, K.-H.; Breitmaier, E. *Chem. Ber.* **1973**, *106*, 1736. Ohta, K.; Iwaoka, J.; Kamijo, Y.; Okada, M.; Nomura, Y. *Nippon Kagaku Kaishi* **1989**, *9*, 1593.

(14) Boger, D. L.; Mullican, M. D. *J. Org. Chem.* **1984**, *49*, 4033.

Calcd for $C_{11}H_{15}NO_3$: C, 63.14; H, 7.23; N, 6.69. Found: C, 63.25; H, 7.24; N, 6.68.

Methyl 5-Methyl-2,6-dioxobicyclo[3.2.1]octane-1-carboxylate (20a). A solution of **15a** (202 mg, 0.97 mmol) and $Mn(OAc)_3 \cdot 2H_2O$ (520 mg, 1.94 mmol) in 10 mL of ethanol was stirred at 25 °C for 24 h. The reaction was treated with saturated $NaHSO_3$ solution to reduce unreacted Mn(III), diluted with 100 mL of water, and extracted with three portions of CH_2Cl_2. (Reactions run in acetic acid were washed with water and saturated $NaHCO_3$ solution.) The combined organic layers were dried ($MgSO_4$) and concentrated in vacuo to afford 150 mg (74%) of crude **20a**. Flash chromatography on silica gel (5:1 hexane–EtOAc) gave 104 mg (51%) of **20a**: mp 127.5–128 °C (hexane–EtOAc); ^{1}H NMR 3.80 (s, 3), 2.85 (d, 1, J = 19.5), 2.66 (dd, 1, J = 2.5, 19.5), 2.51 (ddd, 1, J = 1, 9, 12), 2.47 (dd, 1, J = 2.5, 12.8), 2.24 (dd, 1, J = 2.5, 12.8), 1.87–1.76 (m, 3), 1.20 (s, 3); ^{13}C NMR 215.3, 204.8, 170.5, 59.7, 52.5, 49.0, 45.0, 44.0, 34.8, 34.7, 19.0; IR (neat) 2920, 2790, 1715 cm^{-1}. Anal. Calcd for $C_{11}H_{14}O_4$: C, 62.84; H, 6.71. Found: C, 62.74; H, 6.75.

Methyl 2-(Cyanoethyl)-6-methyl-3-oxo-6-heptenoate (15b). To a solution of 10 mg of sodium in 2 mL of methanol was added **14**[4] (1.835 g, 10.89 mmol). Acrylonitrile (482 mg, 9.08 mmol) was added slowly over 1 h.[6] The solution was stirred for 18 h, acidified with 10% HCl, and extracted with ether. The organic layers were dried ($MgSO_4$) and concentrated in vacuo to afford 1.993 g (98%) of a mixture of **15b**, unreacted **14**, and dialkylated material. Flash chromatography on silica gel (5:1 hexane–EtOAc) afforded 482 mg (24%) of **15b** as a clear oil: ^{1}H NMR 4.75 (br s, 1), 4.66 (br s, 1), 3.78 (s, 3), 3.72 (t, 1, J = 7.5), 2.88 (td, 1, J = 7.6, 17.7), 2.64 (td, 1, J = 7.6, 17.7), 2.45 (t, 2, J = 7.5), 2.31 (br t, 2, J = 7.5), 2.18 (q, 2, J = 7.5), 1.74 (br s, 3); ^{13}C NMR 202.9, 168.7, 143.7, 118.5, 110.4, 56.3, 52.8, 40.6, 30.9, 23.3, 22.5, 15.0; IR (neat) 2960, 2250, 1750, 1720, 1660 cm^{-1}. Anal. Calcd for $C_{12}H_{17}NO_3$: C, 64.55; H, 7.68; N, 6.27. Found: C, 64.65; H, 7.63; N, 6.31.

Methyl 5-Methyl-2,6-dioxobicyclo[3.3.1]nonane-1-carboxylate (20b). A solution of **15b** (180 mg, 0.80 mmol) and $Mn(OAc)_3 \cdot 2H_2O$ (430 mg, 1.60 mmol) in 8 mL of ethanol was stirred at 25 °C for 24 h. Workup as described above for **20a** afforded 121 mg (67%) of crude **20b**. Flash chromatography on silica gel (5:1 hexane–EtOAc) afforded 14 mg (8%) of **20b**: mp 93–94 °C (hexane–EtOAc); ^{1}H NMR 3.78 (s, 3), 2.75 (ddd, 1, J = 4.8, 7.8, 17), 2.69–2.62 (m, 1), 2.57 (dd, 1, J = 2.6, 13.8), 2.53–2.36 (m, 2), 2.35–2.22 (m, 2), 2.14 (dd, 1, J = 2.6, 13.8), 2.00 (dddd, 1, J = 2.6, 4.8, 7.5, 14.1), 1.88 (ddd, 1 J = 7.8, 9.7, 14.1), 1.19 (s, 3); ^{13}C NMR 213.0, 208.2, 171.6, 56.4, 52.7, 43.7, 41.5, 36.6, 36.2, 34.0, 29.2, 24.1; IR (neat) 2950, 1745, 1710 cm^{-1}. Anal. Calcd for $C_{12}H_{16}O_4$: C, 64.27; H, 7.19. Found: C, 64.15; H, 7.18.

Methyl 2-(Cyanomethyl)-3-oxo-7(*Z*)-decenoate (22a). To a solution of alcohol-free sodium methoxide (1.56 mmol) in 5 mL of ether was added **21**[1c,d] (308 mg, 1.56 mmol) followed by bromoacetonitrile (187 mg, 1.56 mmol).[5] The solution was stirred at 25 °C for 4 h. Workup as described above for **15a** afforded 311 mg (84%) of crude **22a**. Flash chromatography on silica gel (5:1 hexane–EtOAc) afforded 206 mg (56%) of **22a** as a clear oil: ^{1}H NMR 5.43 (ttd, 1, J = 1.5, 7.5, 10.8), 5.26 (ttd, 1, J = 1.5, 7.5, 10.8), 3.88 (t, 1, J = 7.3), 3.81 (s, 3), 2.85 (d, 2, J = 7.5), 2.79 (td, 1, J = 7.5, 18), 2.54 (td, 1, J = 7.5, 18), 2.04 (app sext, 4, J = 7.5), 1.70 (app pent, 2, J = 7.5), 0.96 (t, 3, J = 7.5); ^{13}C NMR 201.1, 167.0, 133.0, 127.4, 117.7, 54.2, 53.3, 41.7, 26.0, 23.2, 20.4, 15.7, 14.2; IR (neat) 2970, 2250, 1750, 1730, 1660 cm^{-1}. Anal. Calcd for $C_{13}H_{19}NO_3$: C, 65.80; H, 8.07; N, 5.90. Found: C, 65.86; H, 8.16; N, 5.81.

Methyl (1α,3aβ,7aα)-1-Ethyl-2,4-dioxooctahydro-3a*H*-indene-3a-carboxylate (24a). A solution of **22a** (106 mg, 0.45 mmol) and $Mn(OAc)_3 \cdot 2H_2O$ (240 mg, 0.90 mmol) in 5 mL of acetic acid was stirred at 25 °C for 22 h. Workup as described above for **20a** afforded 49 mg (46%) of crude **24a**. Evaporative distillation (80 °C (0.1 Torr)) afforded 43 mg (40%) of pure **24a** as a clear oil: ^{1}H NMR 3.74 (s, 3), 2.87–2.68 (m, 2), 2.74 (d, 1, J = 18.5), 2.44 (dd, 1, J = 1.2, 18.5), 2.58–2.50 (m, 1), 2.24–2.14 (m, 1), 2.04–1.72 (m, 4), 1.63 (br app pent, 2, J = 7), 0.93 (t, 3, J = 7.5); ^{13}C NMR 214.5, 204.3, 171.2, 62.7, 52.7, 52.6, 51.6, 43.2, 39.3, 26.5, 23.9, 21.3, 10.9; IR (neat) 2960, 1750, 1720 cm^{-1}. Anal. Calcd for $C_{13}H_{18}O_4$: C, 65.53; H, 7.61. Found: C, 65.13; H, 7.55.

A solution of **22a** (54 mg, 0.23 mmol), $Mn(OAc)_3 \cdot 2H_2O$ (129 mg, 0.46 mmol) and TFA (130 mg, 1.15 mmol) in 3 mL of ethanol was stirred at 25 °C for 21 h. Workup followed by evaporative distillation as described above afforded 31 mg (57%) of pure **24a**.

Methyl 2-(2-Cyanoethyl)-3-oxo-7(*Z*)-decenoate (22b). To a solution of 10 mg of sodium in 5 mL of methanol was added **21**[1c,d] (2.219 g, 11.19 mmol). Acrylonitrile (540 mg, 10.17 mmol) was added slowly over 2 h.[6] The solution was stirred for 18 h and worked up as described above for **15b** to afford 2.455 g (89%) of a mixture of **22b**, unreacted **21**, and dialkylated material. Flash chromatography on silica gel (5:1 hexane–EtOAc) afforded 540 mg (20%) of **22b** as a clear oil: ^{1}H NMR 5.41 (ttd, 1, J = 1.5, 7.2, 10.8), 5.27 (ttd, 1, J = 1.5, 7.2, 10.8), 3.77 (s, 3), 3.68 (t, 1, J = 7.5), 2.71 (td, 1, J = 7.5, 17.7), 2.48 (td, 1, J = 7.5, 17.5), 2.43 (t, 2, J = 7.5), 2.17 (app q, 2, J = 7.5), 2.10–2.00 (m, 4), 1.65 (app pent, 2, J = 7.5), 0.96 (t, 3, J = 7.5); ^{13}C NMR 203.5, 168.8, 132.8, 127.6, 118.6, 56.3, 52.7, 41.8, 26.0, 23.4, 23.2, 20.4, 15.0, 14.2; IR (neat) 2930, 2240, 1745, 1715 cm^{-1}.

Methyl (1α,6α)-1-(2-Cyanoethyl)-2-oxo-6-propylcyclohexane-1-carboxylate (25b) and Methyl (1α,4aβ,8aα)-1-Ethyloctahydro-2,5-dioxo-4a(2*H*)-naphthalenecarboxylate (24b). A solution of **22b** (224 mg, 0.89 mmol) and $Mn(OAc)_3 \cdot 2H_2O$ (478 mg, 1.78 mmol) in 10 mL of ethanol was stirred at 25 °C for 18 h. Workup as described above for **20a** afforded 215 mg (96%) of crude product. Flash chromatography on silica gel (20:1 hexane–EtOAc) afforded 35 mg (2%) of a 3.6:1 mixture of **25b** and **24b**, followed by 28 mg (13%) of a 1:4 mixture of **25b** and **24b**, followed by 7 mg (3%) of a 1:8 mixture of **25b** and **24b**.

Data for **24b** were determined from the mixture: ^{1}H NMR 3.77 (s, 3), 3.21 (dddd, 1, J = 0.9, 2.9, 6.3, 11.9), 2.50–2.39 (m, 2), 2.24 (dddd, 1, J = 0.9, 9.5, 13, 13), 2.20–1.50 (m, 10), 0.84 (t, 3, J = 7.5); ^{13}C NMR 209.8 (C=O), 205.4 (C=O), 170.9 (C=O), 60.9 (C), 52.6 (CH_3), 50.6 (CH), 49.1 (CH), 39.8 (CH_2), 37.9 (CH_2), 30.0 (CH_2), 26.1 (CH_2), 25.4 (CH_2), 18.7 (CH_2), 10.3 (CH_3); IR (neat) 2925, 1710 cm^{-1}.

Data for **25b** were determined from the mixture: ^{1}H NMR 3.74 (s, 3), 2.80 (ddd, 1, J = 6.8, 13.1, 14.4), 2.54–2.30 (m, 6), 2.12–1.51 (m, 4), 1.63–1.44 (m, 4), 0.93 (t, 3, J = 7); ^{13}C NMR 207.6, 170.3, 119.7, 63.6, 52.3 (CH_3), 45.8 (CH), 40.3 (CH_2), 32.9 (CH_2), 27.5 (CH_2), 26.7 (CH_2), 25.1 (CH_2), 21.5 (CH_2), 14.2 (CH_3), 13.3 (CH_2); IR (neat) 2930, 2240, 1710 cm^{-1}.

Methyl 2-Acetyl-4-oxospiro[4.4]nonane-2-carboxylate (32a) and Dimethyl 5′-Acetyl-6′,7′-dihydro-2′-methylspiro[cyclopentane-1,7′-5*H*-1-pyridine-3′,5-dicarboxylate] (39). A solution of **28a**[5] (281 mg, 1.81 mmol), methylenecyclopentane (149 mg, 1.81 mmol), and $Mn(OAc)_3 \cdot 2H_2O$ (493 mg, 3.63 mmol) in 18 mL of ethanol was stirred at 25 °C for 29 h. Workup as described above for **20a** gave 360 mg (83%) of a mixture of **32a** and **39**. Flash chromatography on silica gel (5:1 hexane–EtOAc) afforded 172 mg of a 3.5:1 mixture of **32a** and **39**. Evaporative distillation (75 °C (0.1 Torr)) of an 84-mg purified portion afforded 56 mg (26%) of **32a** and 22 mg (15% based on consumption of 2 equiv of **28a**) of pure **39** as the residue.

Data for **32a**: ^{1}H NMR 3.79 (s, 3), 2.88 (s, 2), 2.80 (d, 1, J = 14), 2.41 (d, 1, J = 14), 2.23 (s, 3), 1.88–1.54 (m, 8); ^{13}C NMR 218.5, 202.5, 172.4, 60.9, 55.9, 53.1, 43.6, 42.8, 38.2, 38.1, 26.1, 25.8, 25.7; IR (neat) 2960, 1740, 1720 cm^{-1}. Anal. Calcd for $C_{13}H_{18}O_4$: C, 65.53; H, 7.61. Found: C, 65.60; H, 7.63.

Data for **39**: mp 104.5–105 °C (hexane–toluene); ^{1}H NMR 8.24 (s, 1), 3.91 (s, 3), 3.79 (s, 3), 3.11 (d, 1, J = 13.7), 2.14 (d, 1, J = 13.7), 2.83 (s, 3), 2.23 (s, 3), 2.00–1.55 (m, 8); ^{13}C NMR 202.2, 172.4, 170.9, 167.0, 161.8, 136.9 (CH), 129.3, 123.6, 68.6, 54.6, 53.3, 52.2, 45.2, 40.5, 40.2, 26.4, 25.2, 25.1, 25.0. IR (neat) 2920, 1740, 1720, 1600 cm^{-1}; MS (EI) m/z (rel intensity) 345 (30, M^+), 304 (100), 288 (12), 262 (51), 230 (6). Anal. Calcd for $C_{19}H_{23}NO_5$: C, 66.07; H, 6.71; N, 4.06. Found: C, 66.02; H, 6.65; N, 4.02.

A solution of **28a**[5] (103 mg, 0.890 mmol), methylenecyclopentane (73 mg, 0.890 mmol), $Mn(OAc)_3 \cdot 2H_2O$ (477 mg, 1.78 mmol), and TFA (508 mg, 4.45 mmol) in 10 mL of ethanol was stirred at 25 °C for 18 h. Workup as described above afforded 138 mg (65%) of crude **32a** free of **39** as determined by analysis of the ^{1}H NMR spectrum. Flash chromatography on silica gel (10:1 hexane–EtOAc) afforded 62 mg (30%) of **32a**.

A solution of **28a**[5] (106 mg, 0.923 mmol), methylenecyclopentane (76 mg, 0.92 mmol) and $Mn(OAc)_3 \cdot 2H_2O$ (495 mg, 1.84 mmol) in 10 mL of acetic acid was stirred at 25 °C for 2 h. Workup as described above afforded 107 mg (48%) of crude **32a** free of **39** as determined by analysis of the ^{1}H NMR spectrum. Evaporative

distillation (90 °C (0.1 Torr)) afforded 51 mg (23%) of **32a** as a clear oil.

A solution of **28a**[5] (91 mg, 0.79 mmol), methylenecyclopentane (65 mg, 0.79 mmol), $Mn(OAc)_3 \cdot 2H_2O$ (423 mg, 1.58 mmol), $Mn(OAc)_2 \cdot 4H_2O$ (143 mg, 0.79 mmol), and TFA (450 mg, 3.95 mmol) in 8 mL of ethanol was stirred at 25 °C for 28 h. Workup as above afforded 174 mg (92%) of crude **32a** free of **39**. Evaporative distillation (90 °C (0.1 Torr)) afforded 96 mg (51%) of **32a** as a clear oil and 65 mg (35%) of uncharacterizable oligomeric material as residue of the distillation.

Methyl 7-Acetyl-10-oxospiro[4.5]decane-7-carboxylate (32b) and Methyl α-Acetyl-γ-cyano-α-(cyclopentylmethyl)-1-cyclopentene-1-pentanoate (36b). A solution of **28b**[6] (115 mg, 0.67 mmol), methylenecyclopentane (55 mg, 0.67 mmol), and $Mn(OAc)_3 \cdot 2H_2O$ (361 mg, 1.34 mmol) in 7 mL of ethanol was stirred at 25 °C for 6 h. Workup as described above for **20a** afforded 160 mg (98%) of a mixture of **32b** and **36b**. Flash chromatography on silica gel (5:1 hexane–EtOAc) afforded 24 mg (21%) of **36b** as a 1:1 mixture of diastereomers, followed by 66 mg (39%) of **32b**.

Data for **32b**: ^{1}H NMR 3.80 (s, 3), 2.81 (dd, 1, J = 7.2, 17.1), 2.77 (dd, 1, J = 5.0, 14.7), 2.51 (dd, 1, J = 2.2, 14.6), 2.26 (d, 1, J = 14.6), 2.53–2.45 (m, 2), 2.19 (s, 3), 2.06–1.95 (m, 1), 1.80 (ddd, 1, J = 4.8, 7.9, 11.8), 1.68–1.48 (m, 4), 1.43 (ddd, 1, J = 2.2, 4.5, 12), 1.24 (ddd, 1, J = 8, 8, 13); ^{13}C NMR 212.9, 203.4, 172.6, 59.3, 55.0, 52.7, 41.1, 36.3, 35.7, 35.3, 29.9, 25.6, 25.0, 24.2; IR (neat) 2960, 1750, 1720 cm^{-1}. Anal. Calcd for $C_{14}H_{20}O_4$: C, 66.64; H, 7.99. Found: C, 66.66; H, 8.02.

Data for **36b**: ^{1}H NMR 5.56 (br s, 1), 3.79 (s, 0.5 × 3), 3.78 (s, 0.5 × 3), 2.22 (s, 0.5 × 3), 2.16 (s, 0.5 × 3), 2.68–2.52 (m, 1), 2.50–2.39 (m, 1), 2.39–1.96 (m, 8), 1.96–1.80 (m, 2), 1.80–1.40 (m, 8), 1.14–0.98 (m, 2); ^{13}C NMR 204.8 (C), 204.4 (C), 172.2 (2 C), 138.9 (C), 138.7 (C), 128.9 (CH), 128.6 (CH), 121.9 (C), 121.4 (C), 62.3 (2 C), 52.6 (2 CH_3), 39.3 (CH_2), 37.1 (CH_2), 36.0 (CH), 35.9 (CH), 35.7 (CH_2), 35.6 (CH_2), 34.8 (2 CH_2), 34.7 (CH_2), 33.9 (CH_2), 33.8 (2 CH_2), 33.7 (CH_2), 33.5 (CH_2), 32.5 (2 CH_2), 27.3, 26.6, 26.0, and 25.2 (2 CH and 2 CH_3), 24.8 (3 CH_2), 24.7 (CH_2), 23.5 (CH_2), 23.4 (CH_2); MS (EI) m/z (rel intensity) 331 (1, M^+), 313 (11), 254 (39), 198 (14), 169 (65), 129 (100); IR (neat) 2925, 2230, 1750, 1715 cm^{-1}.

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Registry No. 14, 59529-68-9; **15a**, 137393-41-0; **15b**, 137393-42-1; **20a**, 137393-43-2; **20b**, 137393-44-3; **21**, 71203-73-1; **22a**, 137393-45-4; **22b**, 137393-46-5; **24a**, 137393-47-6; **24b**, 137393-48-7; **25b**, 137393-49-8; **28a**, 137393-50-1; **28b**, 105630-56-6; **32a**, 137393-51-2; **32b**, 137393-52-3; **36b** (isomer 1), 137393-53-4; **36b** (isomer 2), 137393-54-5; **39**, 137393-55-6; bromoacetonitrile, 590-17-0; acrylonitrile, 107-13-1; methylenecyclopentane, 1528-30-9.

Supplementary Material Available: ^{1}H NMR spectrum for **22b** and ^{1}H and ^{13}C NMR spectra for **36b** (3 pages). Ordering information is given on any current masthead page.

Synthesis of *p*-Chlorophenols (and -naphthols) from the Thermal Rearrangement of 4-Chlorocyclobutenones

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A systematic study of the reaction of 4-hydroxycyclobutenones with thionyl chloride is reported. A useful model evolves from this study which allows the prediction of the site of chlorination for unsymmetrical examples. The chlorination is envisaged to involve the corresponding homoaromatic carbocation, and the site of chlorination takes place preferentially at the position substituted with the greater cation-stabilizing substituent. Specifically, this follows the general order of allyl > benzyl > alkyl > propargyl. The 4-chlorocyclobutenones prepared in this study were shown to be useful synthetic precursors to highly substituted chlorophenols and chloronaphthols.

Introduction

Reported here are details of the ring expansions of 4-aryl(or alkenyl or alkynyl)-4-chlorocyclobutenones to chlorophenols (Scheme I).[1] These rearrangements provide useful syntheses of highly substituted aromatic compounds and are mechanistically related to the ring expansions of 4-aryl(or alkenyl or alkynyl)-4-hydroxycyclobutenones to hydroquinones and quinones.[2,3]

The generalized transformations outlined here have their genesis in the chemistry of dimethylsquarate (1), a readily available cyclobutenedione that is easily converted to the regioisomeric cyclobutenones **2** and **3** by known methods.[4,5] Surprisingly, these then give the same 4-chloro derivative **4** upon treatment with thionyl chloride/pyridine in methylene chloride. Finally, thermolysis of **4** in refluxing *p*-xylene results in stereoselective ring opening to the conjugated ketene **5** and then to the chlorophenols (or naphthols) **6** upon electrocyclic ring closure.

Formation of **4** from both **2** and **3** suggests the homoaromatic carbocation **7** to be a common intermediate.[6,7] Furthermore, consideration of the substituent effects on the selectivity of the transformation presents a useful paradigm for predicting the site of chlorination of unsymmetrically substituted cyclobutenones. *Specifically, chlorination takes place preferentially at the position*

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