Tetrahedron Letters,Vol.28,No.8,pp 845-848,1987
Printed in Great Britain

0040-4039/87 $3.00 + .00
Pergamon Journals Ltd.

MANGANESE (III) BASED OXIDATIVE FREE-RADICAL CYCLIZATIONS. 3. POLYCYCLIZATION REACTIONS PROCEEDING THROUGH SECONDARY RADICALS.

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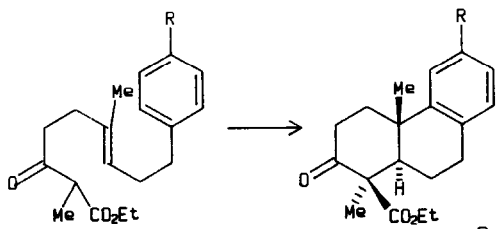
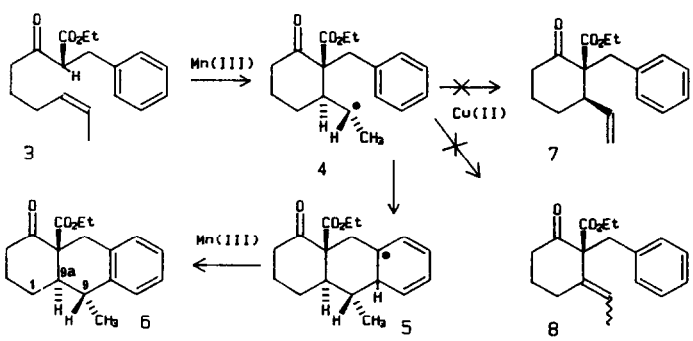
Summary: Oxidative cyclizations of 3, 14, 18 and 21 with $Mn(OAc)_3 \cdot 2H_2O$ give the tricyclic products 6, 15, 19 and 23, respectively, in good yield. These reactions proceed through a monocyclic secondary radical which adds to the benzene ring prior to the second oxidation.

We have recently shown that treatment of the β-ketoester 1 with two equiv. of $Mn(OAc)_3 \cdot 2H_2O$ results in clean oxidative cyclization to give the tricyclic product 2 (50% R=OMe, 90% R=H).[1] In the accompanying communication we present evidence which strongly suggests that this reaction proceeds by cyclization to give the monocyclic tertiary radical which is oxidized to a tertiary cation which then undergoes an intramolecular Friedel-Crafts cyclization to form the tricyclic system.[2] We describe here some new classes of $Mn(OAc)_3 \cdot 2H_2O$ initiated oxidative free-radical cyclizations which proceed through a monocyclic secondary radical which cyclizes to form the second ring prior to oxidation to give a secondary cation.

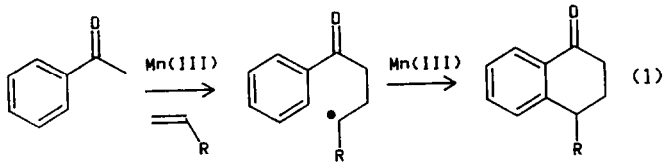


Treatment of the unsaturated β-ketoester 3[3] with two equiv. of $Mn(OAc)_3 \cdot 2H_2O$[6] in acetic acid (0.2 M) for 24 h at 25 °C gave an 83% yield of 6 as a single stereoisomer. The stereochemistry of 6 can be determined unambiguously by analysis of the coupling constants of H_{9a} in the ^1H NMR spectrum. The coupling constant between H_9 and H_{9a} is 10 Hz which indicates that these protons are trans to each other and both pseudoaxial on the central ring. The coupling constants between H_{9a} and $H_{1\alpha}$ and $H_{1\beta}$ are 4 and 11.5 Hz, respectively. The coupling constant of 11.5 Hz indicates that $H_{1\beta}$ and H_{9a} are both axial on the cyclohexanone ring. H_{9a} can only be axial on both rings if the ring fusion is trans. Therefore 6 has the stereochemistry shown.



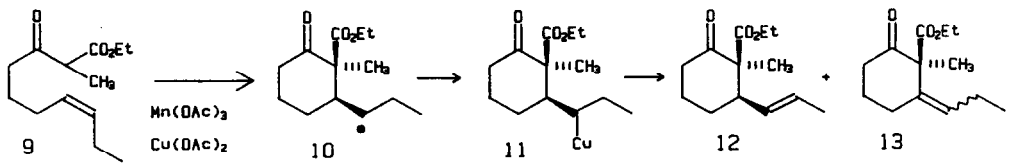
We believe that this reaction occurs by stereospecific cyclization, possibly reversible, to give the intermediate 4, in which the stereochemistry of the double bond is lost, followed by stereospecific cyclization, again possibly reversible, to give the tricyclic intermediate 5 with the more stable equatorial methyl group which is then oxidized by the second equiv. of $Mn(OAc)_3 \cdot 2H_2O$ to give 6. The complete preference for the isomer with an equatorial methyl group was expected since there would be severe steric repulsion between carboethoxy and methyl groups in a 1,3-diaxial relationship.

This oxidative cyclization was modeled on the oxidative addition of acetophenone to an alkene to give a radical which cyclizes to give a tetralone (eq. 1) reported by Heiba and Dessau.[7a] The yields of tetralone obtained by Heiba and Dessau are 40-50% based on $Mn(OAc)_3 \cdot 2H_2O$, but much lower based on ketone or alkene since a large excess of these materials must be used. The oxidative cyclization of 3 proceeds under mild conditions since a β-ketoester is much more easily oxidized than a ketone and proceeds in excellent yield based on 3 as well as $Mn(OAc)_3 \cdot 2H_2O$.



(1)

The oxidative cyclization of simpler substrates such as 9[8] provide evidence for the proposed mechanism. Oxidative cyclization of 9 with $Mn(OAc)_3 \cdot 2H_2O$ leads to the intermediate 10 which abstracts a hydrogen atom, possibly from the solvent or a second molecule of 9, faster than it is oxidized to a cation, to give products with a saturated, propyl side chain.[1] *This result suggests that radical intermediate 4 should abstract a hydrogen atom from the solvent or a second molecule of 3 faster than it is oxidized to a cation. Therefore the cation derived from oxidation of 4 is not a plausible intermediate in the formation of 6.* Moreover, since products with an ethyl side chain were not isolated from 3, the second radical cyclization is much faster than intermolecular hydrogen abstraction.



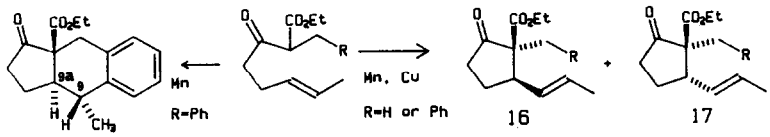
Oxidative cyclization of 9 with two equiv. of $Mn(OAc)_3 \cdot 2H_2O$ and one equiv. of $Cu(OAc)_2$ gave a mixture of 12 (36%) and 13 (13%).[1] The secondary radical 10 reacts with $Cu(OAc)_2$ to give the organocopper intermediate 11 which undergoes β-hydride elimination[9] to give a mixture of 12 and 13. The selective formation of the *E*-isomer of 12 is expected in a *syn* β-hydride elimination. These results indicate, as has been previously shown in related radicals generated by intermolecular reactions,[7] that the oxidation of the radical by $Cu(OAc)_2$ is much faster than intermolecular hydrogen abstraction. The stereochemistry of the monocyclic radical intermediates 4 and 10 is identical. Although the observed isomer is probably the thermodynamic isomer, the difference in energy is not large enough to explain the high degree of stereospecificity which must result from kinetic effects in a highly ordered transition state.

Since both the conversion of 4 to 5 and the oxidation of 10 to a mixture of 12 and 13 are fast relative to intermolecular hydrogen abstraction, we decided to compare the rates of cyclization and oxidation. Heiba and Dessau carried out a similar study on radicals generated from addition of acetophenone to alkenes (see equation 1).[7a] They found that oxidation by $Cu(OAc)_2$ was 240 times faster than cyclization. The radicals which we have generated contain an additional ring which decreases the degrees of rotational freedom and should favor cyclization. Treatment of 3 with $Mn(OAc)_3 \cdot 2H_2O$ and $Cu(OAc)_2$ gave 6 in 66% yield. Neither 7

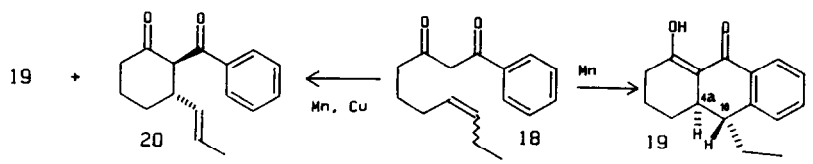
nor **8** was isolated. This indicates that in this case, unlike those described by Heiba and Dessau, cyclization is faster than oxidation by $Cu(OAc)_2$.

Oxidation of **14a**[10] with two equiv. of $Mn(OAc)_3 \cdot 2H_2O$ in acetic acid (0.2 M) for 24 h at 25 °C gave a 74% yield of a 12:2:1 mixture of tricyclic adducts. The structure of the major isomer was shown to be **15** by a combination of spectroscopic and chemical studies. The coupling constant between H_9 and H_{9a} is 12.5 Hz which indicates that these protons are trans to each other and both pseudoaxial on the central ring. The coupling constants between H_{9a} and the vicinal cyclopentane protons are 11.5 and 6.5 Hz. Although this suggest that the ring fusion is trans, the flexibility of the cyclopentane ring precludes an unambiguous assignment. Oxidative cyclization of **14b** with two equiv. of $Mn(OAc)_3 \cdot 2H_2O$ and one equiv. of $Cu(OAc)_2$ gave a 40% yield of a 2.5:1 mixture of **16b** and **17b**. The stereochemistry of the ring fusion of **15** is assigned to be the same as that of the major isomer **16b** since these two processes diverge after the cyclopentane ring is formed.

Oxidative cyclization of **14a** in the presence of $Cu(OAc)_2$ gave a 50% yield of **16a**. Therefore oxidation of the intermediate radical is much faster than the second cyclization reaction. This result is the opposite of that obtained in the oxidative cyclization of **3**, in which cyclization of **4** to **5** is much faster than oxidation to give **7** or **8**. The $Cu(OAc)_2$ oxidations to give **7** and **16** should occur at similar rates. On the other hand, the cyclization to give **15** should be slower than cyclization of **4** to give **5** since a relatively strained *trans*-fused indanone is being formed.

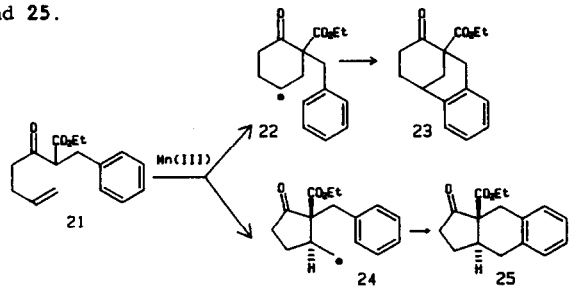


Alkylation of the dianion of benzoylacetone with *Z*- or *E*-1-bromo-3-hexene gave *Z*- and *E*-**18** in 80 and 89% yield, respectively. Oxidative cyclization of either *Z*- or *E*-**18** with $Mn(OAc)_3 \cdot 2H_2O$ as described above gave **19** in 58 and 85% yield, respectively, as the sole isolable product. The coupling constant of 13.5 Hz between H_{4a} and H_{10} establishes that the two hydrogens are trans diaxial. The stereoselective formation of **19** from either isomer of **18** indicates that the intermediate monocyclic radical has a long enough lifetime to permit complete rotational equilibrium. Attempted oxidation of the analog of **18** containing one fewer methylene groups between the ketone and double bond led to a complex mixture of products. This is presumably due to overoxidation, since we have previously shown that enolizable cyclopentanone carboxylate esters are oxidized at least as fast as the precursor acyclic β-ketoester.[1] Oxidative cyclization of *Z*-**18** with two equiv. of $Mn(OAc)_3 \cdot 2H_2O$ and one equiv. of $Cu(OAc)_2$ gave a mixture of **19** (35%) and **20** (18%) indicating that in this case cyclization of the intermediate radical and $Cu(OAc)_2$ oxidation to give **20** occur at similar rates.

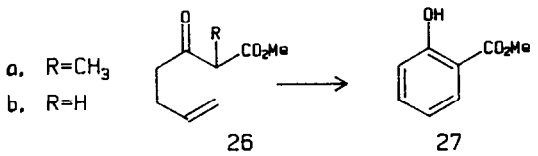


Oxidation of **21** with $Mn(OAc)_3 \cdot 2H_2O$ gave a 55% yield of a 9:3:1 mixture of **23**, **25** and an unidentified compound which is presumably the stereoisomer of **25**. Oxidative cyclization thus leads to a roughly 9:4 mixture of the endocyclic secondary radical **22** and the exocyclic primary radical **24**. The cyclizations of substituted 5-hexenyl radicals are known to give either

cyclohexyl and/or cyclopentylmethyl radicals depending on the substituents and reaction conditions.[11] The structure of **25** was established by the close proximity of its ^{1}H and ^{13}C NMR spectrum to that of **15**. The ketone carbon absorbs at 213.7 δ in the ^{13}C NMR spectrum establishing that the ketone is a cyclopentanone. The ketone carbon of **23** absorbs at 208.8 δ, a value consistent with a cyclohexanone but not a cyclopentanone. Oxidation of **21** with two equiv. of $Mn(OAc)_3 \cdot 2H_2O$ and one equiv. of $Cu(OAc)_2$ gave a 50% yield of a complex mixture containing ≈50% of **23** and **25**.



We examined the oxidation of **26a** with two equiv. of $Mn(OAc)_3 \cdot 2H_2O$ and one equiv. of $Cu(OAc)_2$ to determine if the intermediate cyclohexyl radical could be oxidatively trapped to give a cyclohexenone. A complex largely polymeric mixture was obtained presumably due to over oxidation of the initial product. This observation led us to explore the oxidation of **26b** with four equiv. of $Mn(OAc)_3 \cdot 2H_2O$ and one equiv. of $Cu(OAc)_2$ which led cleanly to methyl salicylate (**27**) in 78% yield. This oxidative cyclization thus provides what should be a general new route to salicylic acid derivatives from acyclic precursors.[12]



The clean cyclizations to form **6**, **15** and **19** indicate that the radical polycyclizations initiated by $Mn(OAc)_3 \cdot 2H_2O$ oxidation proceed in synthetically useful yields in a predictable fashion. We are continuing our development of this cyclization and are exploiting it in synthesis. We are currently exploring the scope of the novel oxidative cyclization to generate methyl salicylate derivatives from acyclic precursors.

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(Received in USA 20 October 1986)