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Termination of Mn(III)-Based Oxidative Cyclizations by Trapping with Azide

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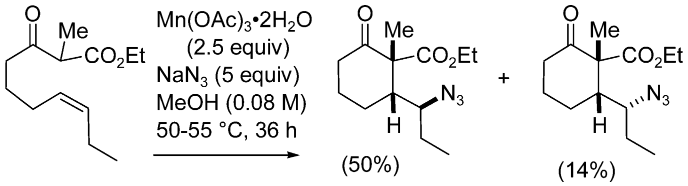
ABSTRACT

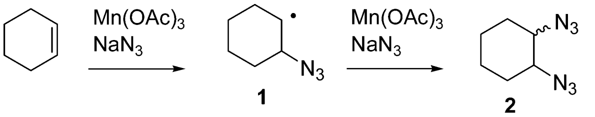


The radicals formed in Mn(III)-based oxidative free-radical cyclizations of *β*-keto esters and malonate esters can be trapped with sodium azide and Mn(III) to give cyclic and bicyclic azides in 30–80% yield. Reduction of the azide gives bi- and tricyclic lactams.

Renaud has recently shown that azidation of alkyl radicals can be achieved by treatment of alkyl iodides and dithionocarbonates with ethanesulfonyl azide in the presence of dilauroyl peroxide or by treatment with benzenesulfonyl azide and hexabutylditin in the presence of a radical initiator (eq 1).[1]

$$R^{\bullet} + R^1SO_2N_3 \rightarrow RN_3 + R^1SO_2^{\bullet} \qquad (1)$$

In 1985, Fristad reported that reaction of $Mn(OAc)_3{\cdot}2H_2O$ and sodium azide with alkenes in HOAc at 85−116 °C affords 1,2-diazides such as **2** (eq 2).[2] An azide anion is oxidized to an azide radical, which adds to an alkene to give a β-azidoalkyl radical such as **1**. This radical reacts with an azide anion and Mn(III) to give 1,2-diazide **2**. We found that this diazidation can be carried out under milder conditions at −20 to 25 °C and in higher yield by using a 9:1 mixture of MeCN and TFA as the solvent.[3]



(2)

We were interested in exploring the possibility of trapping Mn(III)-based oxidative free radical cyclizations[4] to form products such as **8** in Scheme 1 by reaction of radicals such as **7** with an azide anion and Mn(III). This would constitute an attractive procedure for the introduction of nitrogen into the products of mono- and tandem oxidative cyclization reactions. Despite the precedent for this reaction in the formation of **2** from **1**, there were potential concerns with this proposed scheme.

The oxidation of substrate **3** to give radical **4** must be much faster than the oxidation of an azide anion to an azide radical, which would lead to the formation of diazide **6**. This is likely to be the case for 1,3-dicarbonyl compounds such as **3**, but not for simple ketones or acetic acid, which are oxidized at higher temperatures than an azide anion. Radical **4** can react with an azide anion and Mn(III) to give the acyclic azide **5**. This product will be formed if the cyclization of electrophilic radical **4** to give **7** is slower than the oxidative reaction of **4** with azide anion to give **5**. For instance, both acyclic and

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[1] (a) Ollivier, C.; Renaud, P. *J. Am. Chem. Soc.* **2000**, *122*, 6496−6497. (b) Ollivier, C.; Renaud, P. *J. Am. Chem. Soc.* **2001**, *123*, 4717−4727. (c) Renaud, P.; Ollivier, C.; Panchaud, P. *Angew. Chem., Int. Ed.* **2002**, *41*, 3460−3462. (d) Masterson, D. S.; Porter, N. A. *Org. Lett.* **2002**, *4*, 4253−4256. (e) Ollivier, C.; Renaud, P. In *Radicals in Organic Synthesis: Applications*; Renaud, P., Sibi, M. P., Eds.; Wiley-VCH: Weinheim, Germany, 2001; Vol 2, pp 107−108.

[2] Fristad, W. E.; Brandvold, T. A.; Peterson, J. R.; Thompson, S. R. *J. Org. Chem.* **1985**, *50*, 3647−3649.

[3] Snider, B. B.; Lin, H. *Synth. Commun.* **1998**, *28*, 1913−1922.

[4] (a) Snider, B. B. *Chem. Rev.* **1996**, *96*, 339−363. (b) Melikyan, G. G. *Org. React.* **1997**, *49*, 427−675.

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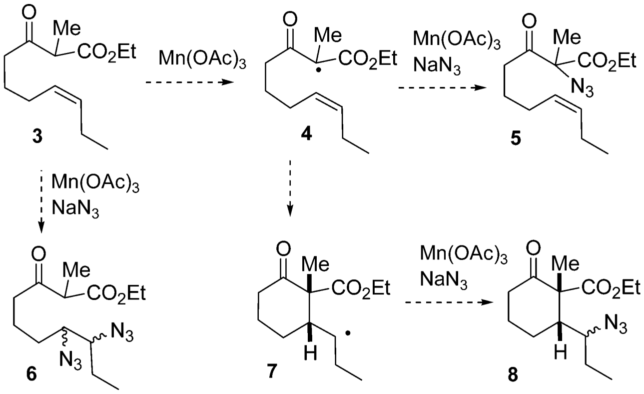
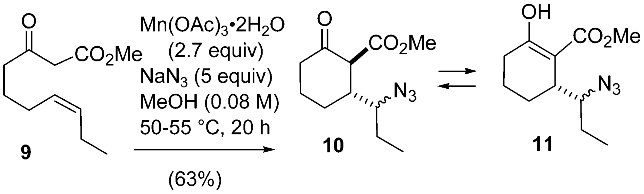
Scheme 1. Proposed Trapping with Azide



cyclic chlorides analogous to **5** and **8** are formed in oxidative cyclizations carried out with $Mn(OAc)_3\cdot 2H_2O$ and LiCl or $CuCl_2$.[5]

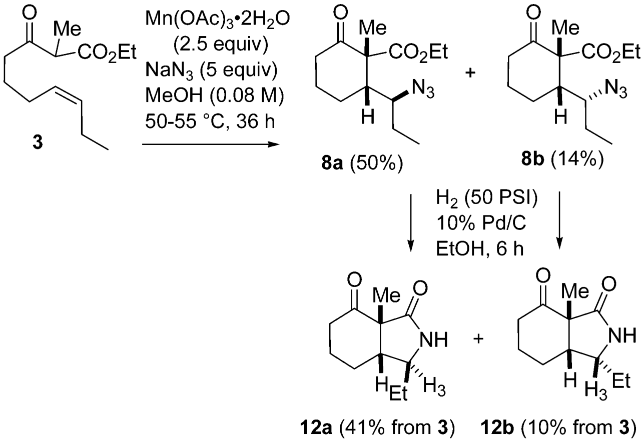
Initial trial reactions were carried out with β-keto ester **9**.[6] Reaction of **9** in acetic acid with $Mn(OAc)_3\cdot 2H_2O$ and NaN_3 affords less than 15% of the desired azide **10** (Scheme 2). Addition of KOAc or TFA does not improve the yield. Reaction in MeCN with or without TFA provides <30% of **10** and some diazide analogous to **6**. No **10** is obtained in trifluoroethanol. Eventually we found that the formation of **10** as a (3:2) mixture of diastereomers can be achieved by oxidation with 2.5 equiv of $Mn(OAc)_3\cdot 2H_2O$ in MeOH containing 5 equiv of NaN_3 in an oil bath kept at 50−55 °C for 20 h. Reaction in MeOH at reflux is faster, but the yields are lower. Attempted purification by flash chromatography affords a complex mixture of **10** and the enol tautomer **11**.

Scheme 2



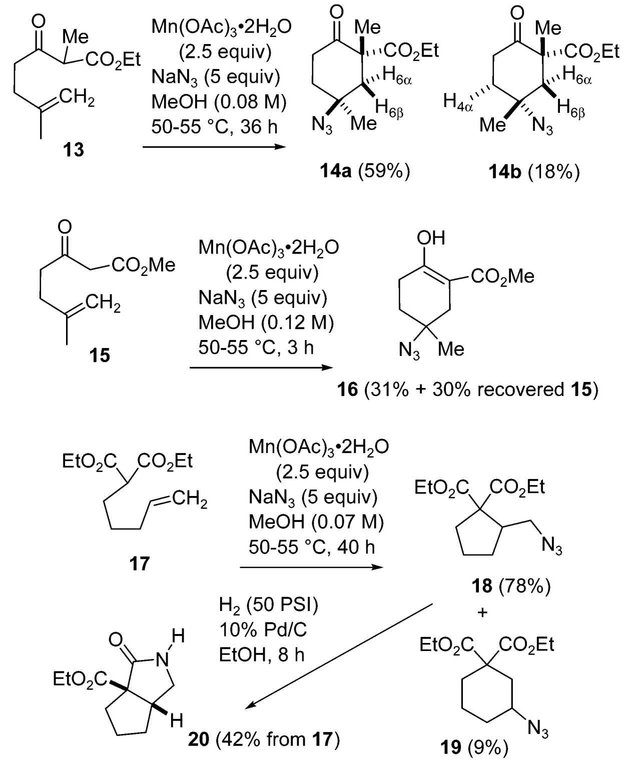
Equally good results were obtained in MeOH with α-methyl-substituted β-keto ester **3**,[6] which affords 50% of azide **8a** and 14% of epimeric azide **8b** (Scheme 3). The structures were established by hydrogenation[7] (50 psi) of the crude mixture over 10% Pd/C in EtOH to afford 41% of lactam **12a** and 10% of lactam **12b**. The stereochemistry of the ring fusion was assigned by analogy to oxidative cyclization of **3** with other trapping reagents.[6] The stereochemistry of the azide was assigned by a NOE observed between H_3 and the ring fusion methyl group in **12b**.

Scheme 3



Tertiary azides can be formed equally well in 6-*endo* cyclizations. Oxidative cyclization of **13**[8] affords 59% of azide **14a** and 18% of azide **14b** (Scheme 4). The stereochemistry was assigned on the basis of a careful consideration of conformational preferences, NOEs, and coupling constants. The minor isomer **14b** strongly prefers a chair conformation with the two larger methyl groups equatorial.

Scheme 4



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(5) Snider, B. B.; Patricia, J. J.; Kates, S. A. *J. Org. Chem.* **1988**, *53*, 2137−2143.

(6) Kates, S. A.; Dombroski, M. A.; Snider, B. B. *J. Org. Chem.* **1990**, *55*, 5, 2427−2436.

(7) Lindstrom, K. J.; Crooks, S. L. *Synth. Commun.* **1990**, *20*, 2335−2337.

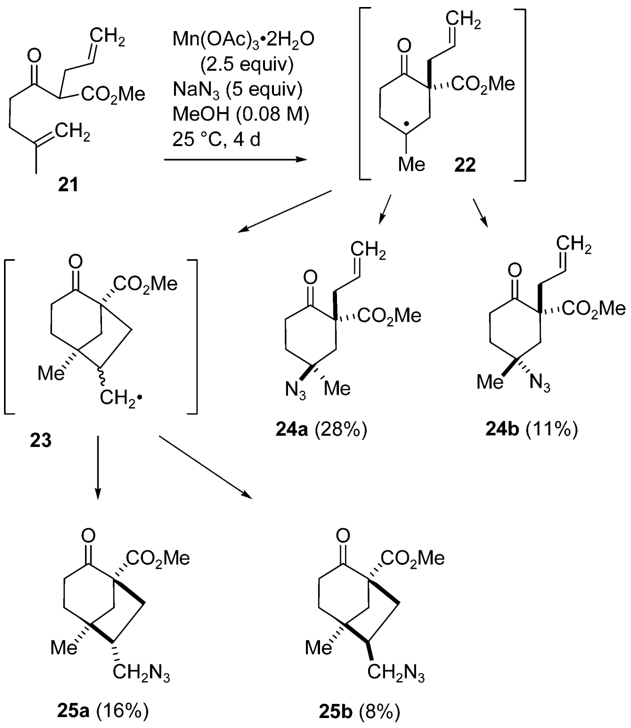
(8) Rao, E. S.; Yadav, J. S. *Ind. J. Chem.* **1986**, *25B*, 1174−1175.

A 3.6 Hz four-bond W-coupling constant is observed between $H_{4\alpha}$ and $H_{6\alpha}$. NOEs are observed between both equatorial methyl groups and both $H_{6\alpha}$ and $H_{6\beta}$. In the major azide **14a**, a NOE is observed between $H_{6\alpha}$ and the C_5−Me group and between $H_{6\beta}$ and the C_1−Me group, indicating that the methyl groups are trans. Oxidative cyclization of **15**[9] proceeds more rapidly but gives only 31% (43% based on recovered **15**) of cyclic azide **16**, which is isolated as the enol tautomer.

Oxidative cyclization of **17**[10] provides an 87% yield of an inseparable 9:1 mixture of 5-*exo* cyclization product **18** and 6-*endo* cyclization product **19**, as expected.[10] Hydrogenation[7] (50 psi) of the crude mixture over 10% Pd/C in EtOH provides bicyclic lactam **20** in 42% overall yield.

Several intriguing features of this reaction emerge from an examination of the tandem oxidative cyclization−azide trapping of β-keto ester **21**.[11] Oxidative cyclization in MeOH at 25 °C for 4 days yields monocyclic azides **24a** (28%) and **24b** (11%) and bicyclic azides **25a** (16%) and **25b** (8%) (Scheme 5). The stereochemistry of the monocyclic azides **24a** and **24b** was assigned by analogy to azides **14a** and **14b**. In **14b** and **24b**, the downfield H_3 absorbs as a ddd (J = 14, 14, 6) at δ 2.99−3.02, while the downfield H_3 of **14a** and **24a** absorbs as a multiplet at δ 2.6−2.7. We have previously established by trapping radical **23** with hydrogen and halides that cyclization of tertiary radical **22** gives **23** as a 2:1 mixture of *exo* and *endo* $CH_2^{\bullet}$ radicals[11] that will lead to the observed 2:1 mixture of *exo* product **25a** and *endo* product **25b**. Analysis of the ^{13}C NMR spectra confirms the stereochemical assignment.[11] C_8 and the C_5-Me group are shifted upfield from δ 48 and 25 in **25b** to δ 43 and 21 in **25a** due to shielding by the *exo* gauche CH_2N_3 group. Similarly, C_4 is shifted upfield from δ 41 in **25a** to δ 33 in **25b** due to shielding by the *endo* gauche CH_2N_3 group.

Scheme 5



Initially, the reaction was run for 20 h at 50−55 °C as with other cyclizations. Very little **24a** is observed under these reaction conditions. Cyclohexanone **24a**, with the azide and 2-propenyl group on the same face of the cyclohexane ring, undergoes a thermal 1,3-dipolar cycloaddition to give a triazoline that reacts further to give a complex mixture of products.[12] Pure **24a** decomposes on heating for 12 h in MeOH at 50−55 °C. Monocyclic azide **24b** and bicyclic azides **25a** and **25b** are stable to these conditions.

Mn(III)-based oxidative cyclization of **21** with $Cu(OAc)_2$ yields only the alkene formed by oxidative elimination from bicyclic radical **23**. No monocyclic products are obtained even though Cu(II) reacts with radicals with rate constants of $>10^6$ sec^{-1}.[4] Since monocyclic azides **24** are the major product, reaction of an azide anion with tertiary radical **22** must occur with a rate constant of close to 10^7 sec^{-1}.

We then explored the effect of additives and other sources of azide on the ratio of monocyclic products **24** to bicyclic products **25**, which is 65:35 in MeOH. To our surprise, a 91:9 mixture of **24** and **25** is formed with 5 equiv of $TMSN_3$, instead of NaN_3, at 50 °C for 2 h. We hypothesized that $TMSN_3$ reacts with MeOH to give MeOTMS and HN_3 and that the increased percentage of **24** formed with $TMSN_3$ might be due to the decrease in pH. Carrying out the oxidative cyclization of **21** with 5 equiv of NaN_3 and 5 equiv of various acids and bases established that this was the case. At low pH ($ClCH_2CO_2H$), the same 91:9 mixture is obtained as with $TMSN_3$. Formation of **24** is less favored with HOAc (79:21), while bases $NaHCO_3$ (55:45), NaOAc (48:52), and Na_2CO_3 (48:52) favor the formation of bicyclic adducts **25**. Alkyl radicals are nucleophilic and may therefore react more rapidly with HN_3 than with azide anion.

We were disappointed to find that oxidative cyclization of **26**[6] in MeOH containing 5 equiv of $ClCH_2CO_2H$ affords only 11% of azide **29** (Scheme 6). Even poorer results were obtained without $ClCH_2CO_2H$. This result was quite surprising because oxidative cyclization of **26** in HOAc with oxidative termination by $Cu(OAc)_2$ affords 78% of **27**.[6] However, oxidative cyclization of **26** in MeOH with $Cu(OAc)_2$ proceeds in poor yield, indicating that, for reasons that are obscure, the use of HOAc as the solvent is important for this cyclization. Oxidative cyclization in HOAc with 5 equiv of NaN_3 affords a mixture of 24% of azide **28**, 18% of azide **29**, and 17% of reduction product **30**. The structure of **30** was established by preparation of an authentic sample by hydrogenation of **27**. The stereochemistry of **28** and **29**

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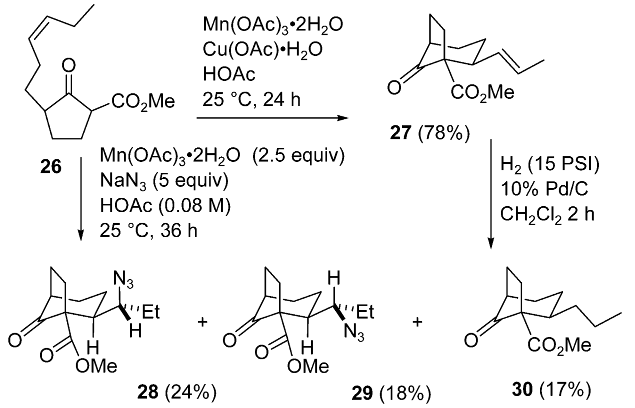
(9) Snider, B. B.; Patricia, J. J. *J. Org. Chem.* **1989**, *54*, 38−46.

(10) Snider, B. B.; McCarthy, B. A. *J. Org. Chem.* **1993**, *58*, 6217−6223.

(11) Dombroski, M. A.; Kates, S. A.; Snider, B. B. *J. Am. Chem. Soc.* **1990**, *112*, 2759−2767.

(12) (a) Laatsch, H.; Ernst, B. P.; Noltemeyer, M. *Liebigs Ann. Chem.* **1996**, 731−737. (b) Eguchi, S.; Suzuki, T.; Toi, N.; Sasaki, T. *Heterocycles* **1990**, *30*, 237−240.

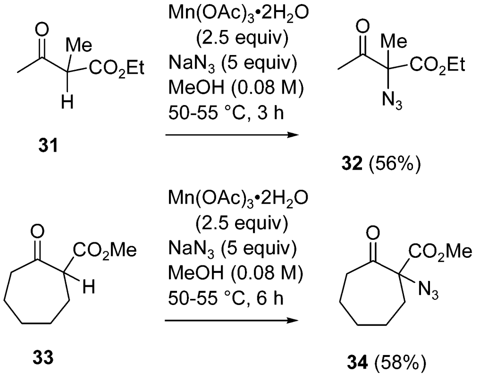
Scheme 6



was tentatively assigned on the basis of conformational analysis and vicinal coupling constants. The most stable side chain conformer of both isomers should be the staggered one with the ethyl group away from the ester and two-carbon bridge as shown. The vicinal coupling constant between the hydrogens shown should be smaller in **28** with a 60° torsion angle between the hydrogens (6.3 Hz) than in **29** with a 180° torsion angle (8.8 Hz). The successful azidation of **26** in HOAc is in marked contrast to the azidations of **3** and **9**, which are much more successful in MeOH. The formation of **30** indicates that trapping with azide is less efficient in HOAc. This may be due to the decreased solubility of NaN_3 in HOAc.

Finally, we explored whether β-keto ester radicals analogous to **4** that are formed by oxidation of a saturated β-keto ester, and therefore cannot cyclize, will react with azide anion and Mn(III) to form an α-azido β-keto ester. These azides have previously been prepared in 50−70% yield by reaction of β-keto esters with NBS in CCl_4 and reaction of the crude bromide with NaN_3 in DMSO.[13] Reaction of ethyl 2-methylacetoacetate (**31**) with $Mn(OAc)_3{\cdot}2H_2O$ and NaN_3 in MeOH at 50−55 °C for 3 h yields azide **32** (56%) (Scheme 7).[14] A similar reaction of methyl 2-oxocycloheptanecarboxylate (**33**) affords azide **34** (58%).[13] However, attempted azidation of methyl 2-oxocyclopentanecarboxylate and ethyl 2-oxocyclohexanecarboxylate under these conditions yields complex mixtures containing less than 10% of the azide. The reasons for the efficient formation of the azide from some β-keto esters but not others are obscure but may be related to the fact that some similar radicals undergo facile oxidative elimination to alkenes that are very good Michael acceptors.[15]

Scheme 7



In conclusion, we have shown that the radicals formed in Mn(III)-based oxidative free-radical cyclizations of β-keto esters and malonate esters can be trapped with NaN_3 and Mn(III) to give cyclic and bicyclic azides in 30−80% yield. Reduction of the azide forms primary amines that react with a proximate ester to form bi- and tricyclic lactams.

Acknowledgment. We thank the National Institutes of Health (GM-50101) for generous financial support.

Supporting Information Available: Detailed experimental procedures, discussion of stereochemical assignments, and copies of NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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[13] Benati, L.; Nanni, D.; Sangiorgi, C.; Spagnolo, P. *J. Org. Chem.* **1999**, *64*, 7836−7841.

[14] Benati, L.; Nanni, D.; Spagnolo, P. *J. Org. Chem.* **1999**, *64*, 5132−5138.

[15] (a) Citterio, A.; Santi, R.; Fiorani, T.; Strologo, S. *J. Org. Chem.* **1989**, *54*, 2703−2712. (b) Snider, B. B.; Smith, R. B. *Tetrahedron* **2002**, *58*, 25−34.