



A concise construction of an erythrinane skeleton using Mn(III)/Cu(II)-mediated oxidative radical cyclization of α -methylthio amides

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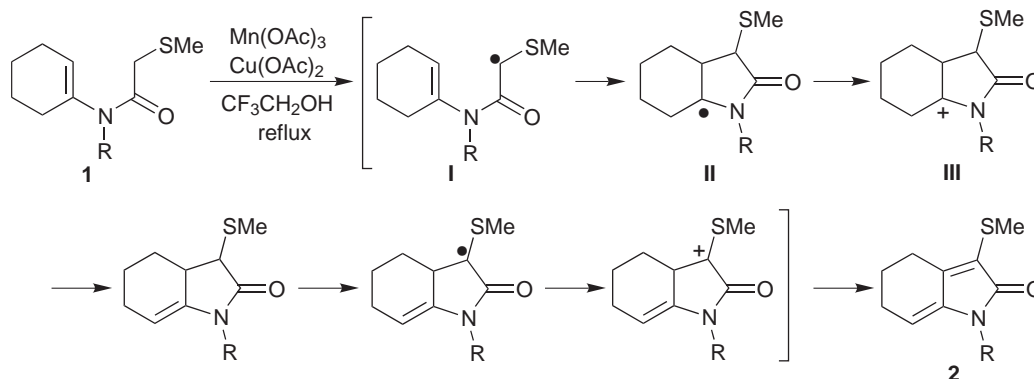
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Abstract—Oxidative radical cyclizations of enamide **3** with Mn(OAc)₃ in the presence of Cu(II) were examined. When Cu(OAc)₂ was used as an additive, 4-acetoxyerythrinane derivative **5** was formed, whereas the use of Cu(OTf)₂ afforded simple erythrinane **6**. © 2001 Elsevier Science Ltd. All rights reserved.

Oxidative radical cyclization with Mn(III) has attracted considerable attention in recent years.^{1,2} In a previous paper, we reported that treatment of *N*-(cyclohex-1-enyl)- α -(methylthio)acetamides **1** with Mn(OAc)₃ in the presence of Cu(OAc)₂ produced methylthio-substituted carbamoylmethyl radicals **I**, which cyclized to give tetrahydroindol-2-one derivatives **2**.^{3,4} One possible explanation for the formation of **2** from **1** may involve the 5-*endo-trig* cyclization of radicals **I** giving **II** followed by sequential oxidations via cations **III** as outlined in Scheme 1. In the present study, we examined the reaction of enamide **3** having a 2-(3,4-dimethoxyphenyl)-

ethyl group on the nitrogen atom, and a concise route to erythrinane derivatives using this method is described in this paper.

We initiated our investigation by examining the reaction of enamide **3**⁵ under conditions similar to those described for **1**. When enamide **3** was treated with Mn(OAc)₃ (6 equiv.) in the presence of Cu(OAc)₂ (1 equiv.) in boiling CF₃CH₂OH for 9 h, compound **4** was obtained in 72% yield along with small quantities of the starting material **3** (19%) and erythrinane derivative **5** (mp 156–157°C) (6%). A similar reaction of **3** with a



Scheme 1.

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much larger amount (10 equiv.) of $\text{Mn}(\text{OAc})_3$ in the presence of $\text{Cu}(\text{OAc})_2$ (1 equiv.) for 13 h resulted in an increase in yield (52%) of erythrinane derivative **5** with a decrease in yield of **4** (39%).⁶

The structure of **5** was deduced from its spectral properties. The IR spectrum (CHCl_3) showed bands at 1735 and 1675 cm^{-1} , which were clearly indicative of an ester group and an unsaturated five-membered lactam, respectively. The ^1H NMR spectrum exhibited two singlets due to MeCO_2 and MeS groups at δ 2.00 and 2.49, respectively, and a signal due to the methine proton on C-4 appeared as a doublet ($J=2.6\text{ Hz}$) at δ 5.34, indicating the axial nature of the AcO group on C-4. The ^{13}C NMR spectrum exhibited a signal at δ 68.34 ascribable to the quaternary carbon atom on C-5. The structure of **5** was finally established by X-ray crystallographic analysis as shown in Fig. 1.⁷

When compound **4** was further treated with $\text{Mn}(\text{OAc})_3$ (4 equiv.) in the presence of $\text{Cu}(\text{OAc})_2$ (1 equiv.) in boiling $\text{CF}_3\text{CH}_2\text{OH}$, erythrinane **5** was obtained in 37% yield along with the recovered **4** (57%) after 2 days of reaction.⁸ On the other hand, the use of $\text{Mn}(\text{OAc})_2$ in place of $\text{Mn}(\text{OAc})_3$ in the presence of $\text{Cu}(\text{OAc})_2$ gave

no erythrinane derivative. This was also the case for the use of $\text{Cu}(\text{OAc})_2$ alone, which resulted in recovery of the starting material **4**. These results suggest that the formation of **5** from **3** proceeds as outlined in Scheme 2. Thus, at first enamide **3** gives **4** via enamide **V** in a manner similar to that described for the formation of **2** from **1** (Scheme 1). The carbonyl oxygen atom and the sulfur atom of **4** might then coordinate to $\text{Mn}(\text{OAc})_3$ and $\text{Cu}(\text{OAc})_2$, respectively, with concomitant aromatization by addition of AcOH to give pyrrole **VI**. The subsequent single electron transfer (SET) reaction gives new radical **VII**, which is then oxidized with $\text{Mn}(\text{OAc})_3$ or $\text{Cu}(\text{OAc})_2$ to give the cationic intermediate **VIII** with its resonance form **VIII'**. Finally, axial attack of the 3,4-dimethoxyphenyl group takes place on the cationic species **VIII'** from the opposite face to that of the AcO group to give erythrinane **5**.⁹

We also found that treatment of **3** with $\text{Mn}(\text{OAc})_3$ (6 equiv.) in the presence of $\text{Cu}(\text{OTf})_2$ (1 equiv.) in place of $\text{Cu}(\text{OAc})_2$ as an additive gave another erythrinane derivative **6** (mp $169\text{--}170^\circ\text{C}$, lit.⁵ mp $169.5\text{--}170.5^\circ\text{C}$) in 54% yield as a sole product. Formation of **6** from **3** can be simply rationalized by assuming that an aromatic ring attacks the cationic intermediate **IV**.¹⁰

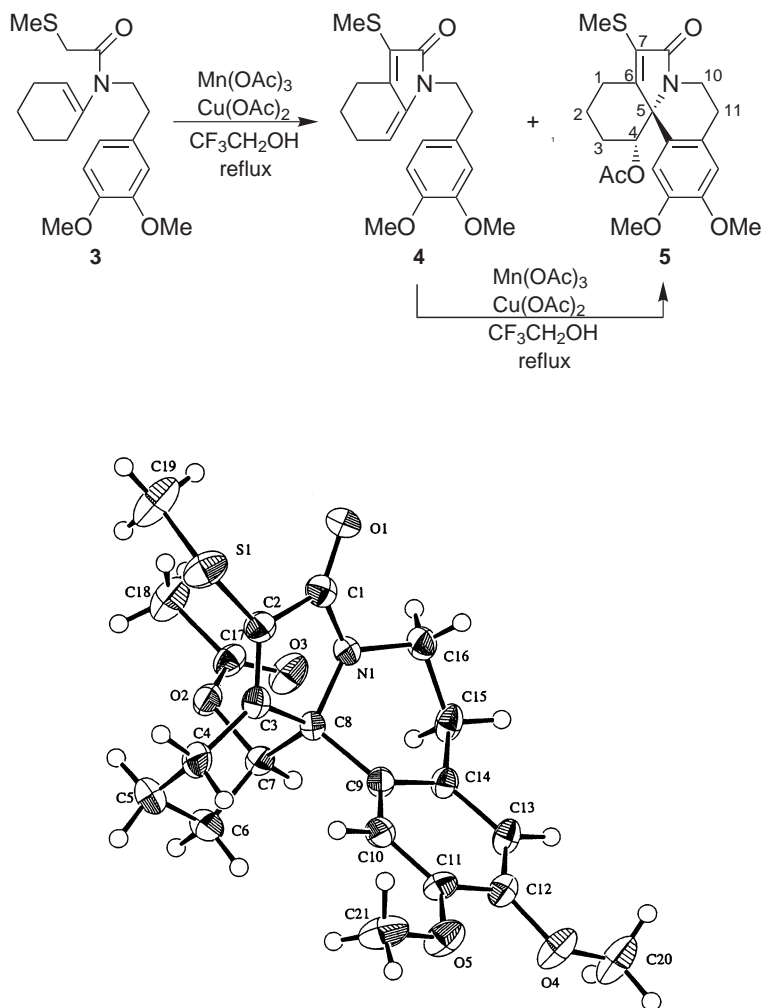
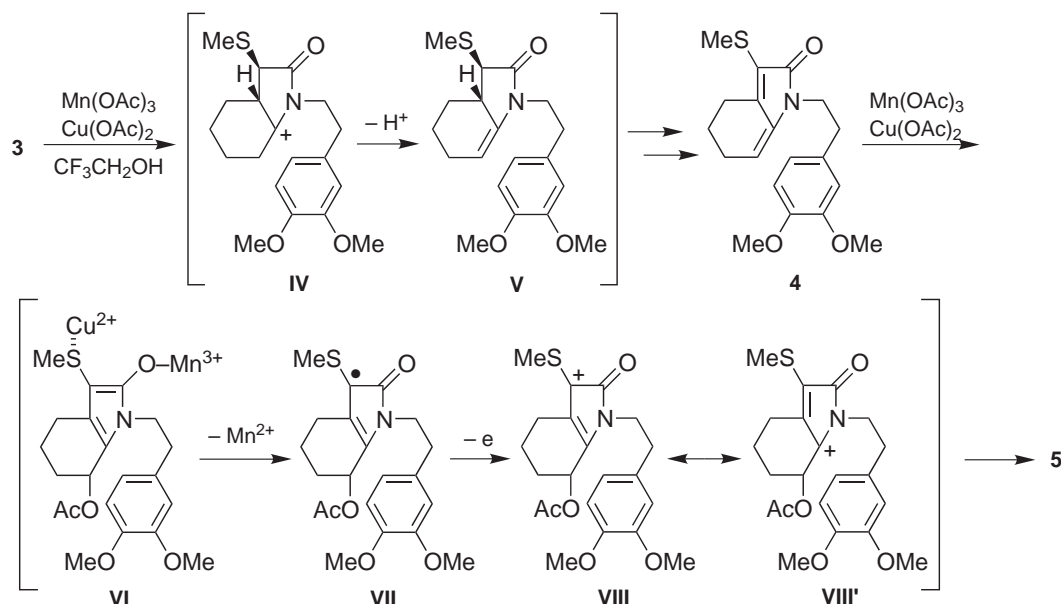
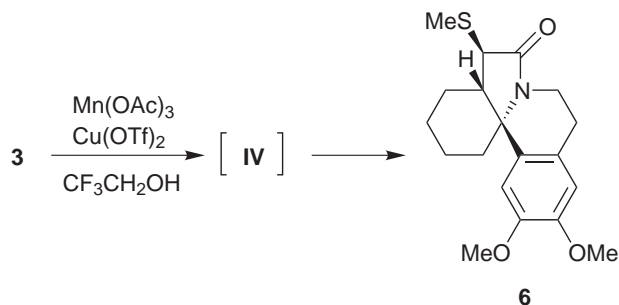


Figure 1. ORTEP drawing of **5**.



Scheme 2.



The difference between the modes of reaction of **3** with $\text{Cu}(\text{OAc})_2$ and $\text{Cu}(\text{OTf})_2$ as an additive may be explained in terms of the difference in the acidities of the reaction systems. When $\text{Cu}(\text{OTf})_2$ was used, enamide **V**, formed by deprotonation of the cationic intermediate **IV**, was readily reprotonated with a strong acid TfOH to give again **IV**. On the other hand, when $\text{Cu}(\text{OAc})_2$ was used, less acidic AcOH could not protonate towards **V**, which then underwent further oxidation to give **4**.

We have shown that oxidative radical cyclization of α -methylthio amides with $\text{Mn}(\text{III})/\text{Cu}(\text{II})$ could be applied to a concise construction of an erythrinane skeleton. Further applications of this type of cascade approach to polycyclic compounds are under intense investigation.

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- Crystal data for **5**: $\text{C}_{21}\text{H}_{25}\text{NO}_5\text{S}$, $M=403.49$, triclinic, space group $P1$, $a=10.913(2)$, $b=11.780(2)$, $c=8.785(3)$ Å, $\alpha=110.02(2)^\circ$, $\beta=104.64(2)^\circ$, $\gamma=83.76(1)^\circ$, $V=1026.5(4)$ Å³, $Z=2$, $\mu(\text{Mo}-\text{K}\alpha)=1.89$ cm⁻¹, $F(000)=428$, $D_c=1.305$ g cm⁻³, crystal dimensions: $0.12\times0.20\times0.22$ mm. A total of 4946 reflections (4717 unique) were collected using the $w-2\theta$ scan technique to a maximum 2θ value of 55° , and 2180 reflections with $I>3\sigma(I)$ were used in the structure determination. Final R and R_w values were 0.066 and 0.081, respectively. The maximum and minimum peaks in the difference map were 0.33 and -0.33 e Å⁻³, respectively.
- The use of $\text{Mn}(\text{OAc})_3$ (4 equiv.) alone also gave **5** in 31% yield together with the starting material **4** (51%). However, this reaction required longer reaction time (3 days).
- Treatment of compound **1** ($\text{R}=\text{CH}_2\text{Ph}$) with a large quantity (10 equiv.) of $\text{Mn}(\text{OAc})_3$ in the presence of $\text{Cu}(\text{OAc})_2$ (1 equiv.) for 15 h provided a complex mixture of products containing **2** ($\text{R}=\text{CH}_2\text{Ph}$). This is probably

the result that the cationic intermediate of type **VIII** (or **VIII'**) decompose under the reaction conditions due to the lack of such nucleophilic aromatic ring in **VIII** (or **VIII'**).

10. Zard and his co-workers reported that Ni/AcOH-mediated reductive radical cyclization of *N*-(cyclohex-1-enyl)-

N-[2-(3,4-dimethoxyphenyl)ethyl]trichloroacetamide gave tetrahydroindol-2-one derivative of type **4** (without MeS group) probably via cationic intermediate similar to **IV**, but afforded no erythrinane derivative. See: Cassayre, J.; Quiclet-Sire, B.; Saunier, J.-B.; Zard, S. Z. *Tetrahedron Lett.* **1998**, 39, 8995.