ORGANIC LETTERS

2003
Vol. 5, No. 12
2063−2066

Oxidative 5-*Endo* Cyclization of Enamides Mediated by Ceric Ammonium Nitrate

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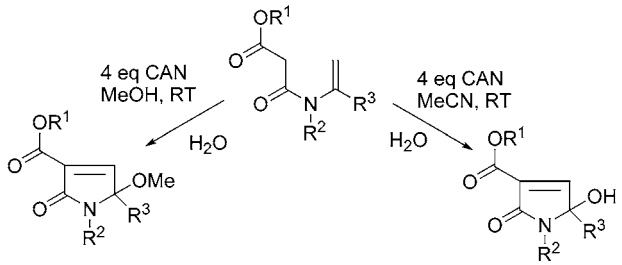
Received March 18, 2003

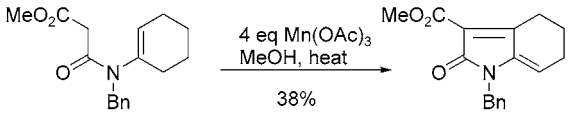
ABSTRACT



Ceric ammonium nitrate mediates the oxidative 5-*endo* radical–polar crossover reactions of *β*-enamide esters to give 5,5-*C*,*O*-disubstituted-*γ*-lactams. Trapping of the intermediate cations leads to 5-hydroxy- or 5-alkoxy-*γ*-lactams depending upon the reaction conditions. The methodology was used to synthesize the basic heterocyclic ring fragments of the natural products L-755,807, Quinolacticin C, and PI-091.

The use of radical cyclization protocols to prepare heterocyclic compounds continues to be widespread.[1] By far the most popular methods for conducting such cyclizations involve the use of Bu_3SnH as a mediator. One distinct disadvantage of this approach is that the cyclizations are reductive in nature. We and others have recently reported the use of Cu(I) halide complexes,[2] nickel metal,[3] or Mn(OAc)$_3$ reagents[4] in unusual oxidative 5-*endo* cyclization reactions. In these reactions functionality is retained during cyclization via an oxidative radical−polar crossover reaction (e.g. Scheme 1). Cerium(IV) compounds represent some of the most notable oxidants among lanthanide reagents. As might be expected for very powerful one-electron oxidants, the chemistry of Ce(IV) oxidations of organic molecules is dominated by radical and radical cation chemistry.[5]

Scheme 1. 5-*Endo* Cyclization Mediated by Mn(OAc)$_3$



Nair and co-workers[6] have carried out a number of studies to compare the reactivity of Mn(OAc)$_3$ with CAN in the oxidative addition of 1,3-dicarbonyl radicals to unactivated

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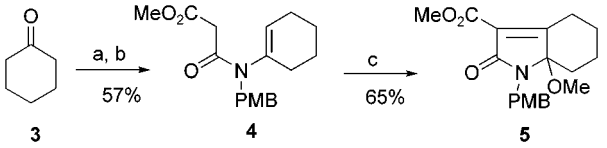
(1) Bowman, W. R.; Fletcher, A. J.; Potts, E. B. S. *J. Chem. Soc., Perkin Trans. 1* **2002**, 2747.
(2) Clark, A. J. *Chem. Soc. Rev.* **2002**, 1.
(3) Cassayre, J.; Quiclet-Sirre, B.; Saunier, J.-B.; Zard, S. Z. *Tetrahedron* **1998**, *54*, 1029.
(4) Davies, D. T.; Kapur, N.; Parsons, A. F. *Tetrahedron* **2000**, *56*, 3941.
(5) Molander, G. A. *Chem. Rev.* **1992**, *92*, 29.
(6) (a) Nair, V.; Mattew, J.; Radhakrishnan, K. C. *J. Chem. Soc., Perkin Trans. 1* **1996**, 1487. (b) Nair, V.; Mattew, J. *J. Chem. Soc., Perkin Trans. 1* **1995**, 187.

10.1021/ol030045f CCC: $25.00
Published on Web 05/09/2003

alkenes, and discovered that CAN was often superior to Mn(OAc)$_3$. More recently, CAN-mediated intermolecular radical reactions in ionic liquids have been reported.[7] Consequently, we decided to investigate whether CAN could be used to mediate 5-*endo-trig* cyclizations of β-enamide esters to give γ-lactams of importance for natural product synthesis.

Our initial experiments examined the cyclization of the β-amido ester precursor **4** (analogous to compound **1** from Scheme 1). Compound **4** was prepared by *N*-acylation of the imine derived from cyclohexanone **3** and *p*-methoxybenzylamine (PMB), with methyl malonyl chloride.[4] Initial reactions of **4** with 2 equiv of CAN in methanol at room temperature gave the bicyclic lactam **5** in only 28% yield. However, the yield of this reaction was found to improve from 28% to 65% when 4 equiv of CAN was employed for 20 min. Addition of greater than 4 equiv was found to have a detrimental effect on the product yield, Scheme 2. Under

Scheme 2. 5-*Endo* Cyclization of **4** by CAN[a]



[a] Reagents and conditions: (a) PMBNH$_2$, Dean−Stark, toluene, reflux; (b) MeO$_2$CCH$_2$COCl, toluene, 0 °C; (c) 4 equiv of CAN, MeOH, rt.

these conditions no deprotection of the PMB group was observed. Interestingly, while the Mn(OAc)$_3$-mediated cyclization of **1** leads to the diene **2**, the analogous CAN-mediated cyclization of **4** furnishes the alkoxy trapped product **5**. Thus, the CAN and Mn(OAc)$_3$ procedures are complementary giving rise to different products.

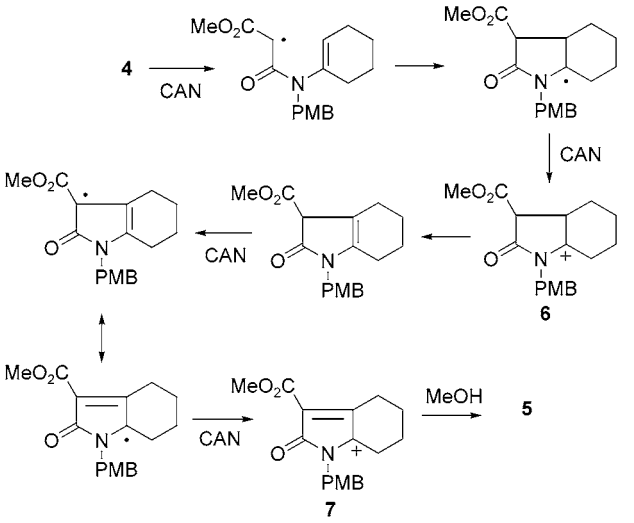
Mechanistically **5** may be formed by initial radical generation from **4** followed by a 5-*endo* cyclization and oxidation to the acyl iminium ion **6** by a second equivalent of CAN. Elimination, followed by a second radical generation and oxidation sequence furnishes the iminium ion **7**, which upon trapping with the solvent furnishes the observed product **5**. This is in keeping with the fact that 4 equiv of CAN was required for efficient reaction. Cyclization of **4** did not proceed in other solvents (such as dichloromethane, 1,2-dichloroethane, benzene, or toluene) at room temperature or at reflux.

The scope and limitation of the procedure was then examined. Cyclization of **8** with use of the standard conditions gave the expected 5-*endo* cyclization product **9** as an inseparable 10:1 mixture of diastereomers (stereochemistry of the major isomer unconfirmed) as well as an unknown minor component (less than 3−4%) in 78% combined yield.

Reaction of the tetralone-derived enamides **10** and **11** proceeded in a slightly different manner. No solvent-trapped products were isolated in either reaction. Instead the fully

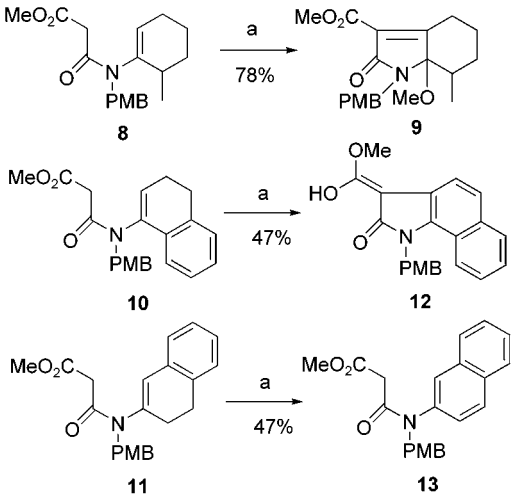
(7) Bar, G.; Bin, F.; Parsons, A. F. *Synth. Commun.* **2003**, 213.

Scheme 3. Proposed Mechanism of 5-*Endo* Cyclization of **4** Mediated by CAN



aromatized structures **12** and **13** were isolated in poor yield (compound **13** was contaminated with less than 5% of an unknown inseparable impurity). Thus for **10** CAN-mediated aromatization occurs after cyclization whereas for **11** cyclization is not observed at all.

Scheme 4[a]



[a] Reagents and conditions: (a) 4 equiv of CAN, MeOH, rt, 20 min.

As part of a progamme toward the synthesis of natural products containing the highly functional 5,5-*C*,*O*-disubstituted-γ-lactam skeleton, such as **14**−**16**,[8] we next investi-

(8) Isolation: (a) L-755, 807: Lam, T. Y. K.; Hensens, D. D.; Ransom, R.; Gaicobbe, R. A.; Polishool, J.; Zinc, D. *Tetrahedron* **1996**, *52*, 1481. (b) PI-091: Kawashima, A.; Yosohimura, Y.; Sakai, N.; Kamigoori, K.; Mizutani, T.; Omura, S. Jpn. Kokai Tokkyo Koho JP 02 62,859; *Chem Abstr.* **1990**, *113*, 113856d. (c) Quinolactacin, C.; Tatsuta, K.; Misawa, H.; Chikauchi, K. *J. Antibiot.* **2001**, *54*, 109.

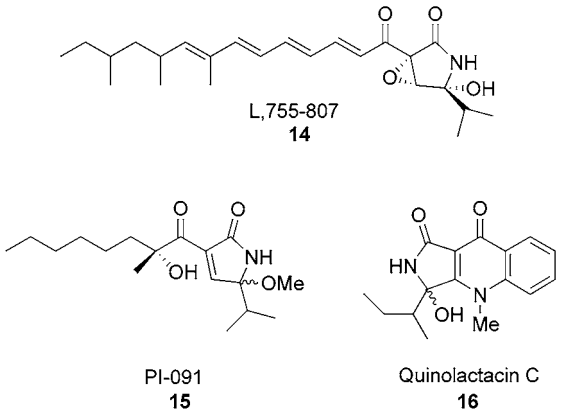
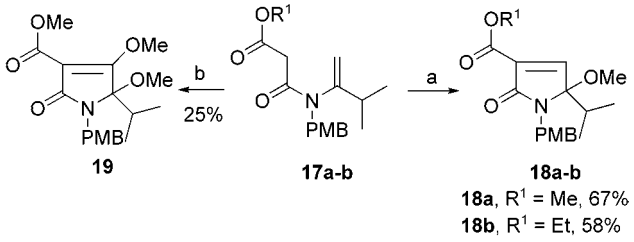


Figure 1. Structures of natural products **14**−**16**.

gated the cyclization of enamides that contained no substitution at the terminal carbon. Hence, cyclization of either the methyl **17a** or ethyl **17b** esters with CAN in MeOH at room temperature for 20 min furnished the desired 5-*endo* products **18a**,**b** in moderate yield (58−67%). We were delighted that the reaction was successful and allowed access to the desired heterocyclic core of the platelet inhibitor PI-091, Scheme 5.

Scheme 5. CAN-Promoted 5-*Endo* Cyclization to the Heterocyclic Core of PI-091 **15**[a]



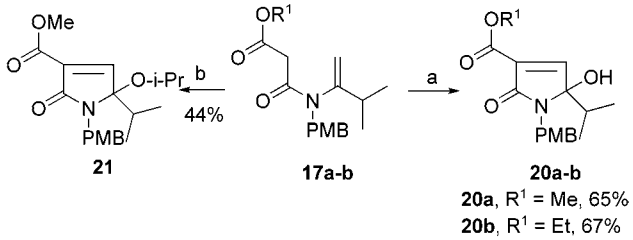
[a] Reagents and conditions: (a) 4 equiv of CAN, MeOH, rt, 20 min; (b) 4 equiv of CAN, MeOH, reflux.

To maximize the yield in the synthesis of **18a** the temperature was increased and **17a** was heated with CAN in MeOH for 2 h at reflux. Under these conditions a 1:1 mixture of **18a** and **19** was isolated in 50% yield. Presumably **19** arises from a Michael addition of MeOH to the unsaturated heterocycle **18a** followed by further CAN-mediated oxidation.

We have recently published a route to the side-chain tetraene fragment of L-755,807, **14**.[9] Consequently, we wished to test our methodology to see if it was applicable for the formation of γ-hydroxylated heterocycles as well as γ-methoxylated heterocycles. In other words, could we mediate the cyclization in the presence of other nucleophiles (e.g. H_2O instead of MeOH). Reaction of both **17a** and **17b**

(9) Clark, A. J.; Ellard, J. M. *Tetrahedron Lett.* **1998**, *39*, 6033.

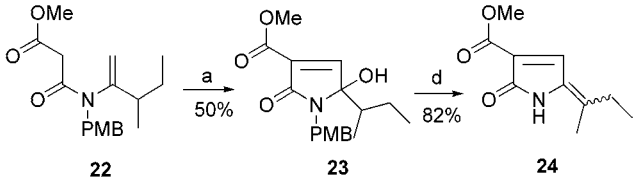
Scheme 6. CAN-Promoted 5-*Endo* Cyclization to the Heterocyclic Core of L,755,807 **14**[a]



[a] Reagents and conditions: (a) 4 equiv of CAN, MeCN, rt, 20 min; (b) 4 equiv of CAN, i-PrOH, rt, 20 min.

with 4 equiv of CAN in acetonitrile as solvent, followed by aqueous workup furnished the desired hydroxy lactams **20a**,**b**. In a similar manner changing the solvent from MeOH to i-PrOH led to the isopropoxy-trapped lactam **21**. Attempts

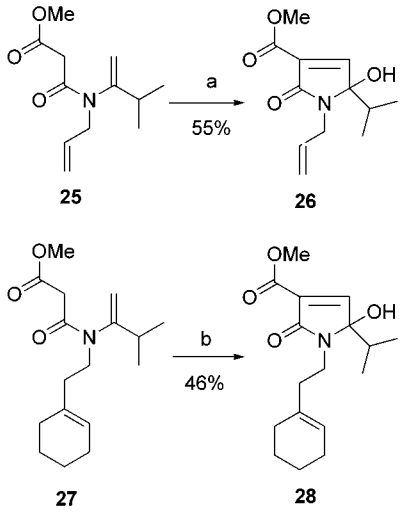
Scheme 7. CAN-Promoted 5-*Endo* Cyclization to the Heterocyclic Core of Quinolactacin C **16**[a]



[a] Reagents and conditions: (a) 4 equiv of CAN, MeCN, rt, 20 min, H_2O; (b) TFA, heat.

to mediate the reactions by using other Ce(IV) salts such as CeO_2 or $Ce(OH)_4$ in MeCN led to unreacted starting material.

Scheme 8. 5-*Endo* CAN-Promoted Cyclization of **25** and **27**[a]



[a] Reagents and conditions: (a) 4 equiv of CAN, MeCN, rt, 20 min; (b) 4 equiv of CAN, MeCN, rt, 20 min, H_2O.

Utilizing our approach it was possible to prepare the analogue **23** of the Quinolactacin C skeleton. Thus treatment of **22** with 4 equiv of CAN in acetonitrile led to the desired hydroxy lactams after aqueous workup (albeit as a 2:1 mixture of diastereomers). Attempts to deprotect the *p*-methoxybenzyl group by using more CAN or TFA furnished the eliminated lactam **24** as a 1.3:1 *E*:*Z* mixture, Scheme 7.

We further tested the scope and limitation of the CAN-mediated 5-*endo* procedure by examining the reaction of the precursor **25**. Cyclization of **25** could in theory proceed either via a 5-*endo* cyclization onto the enamide alkene or by a 5-*exo* cyclization onto the allyl group. Reaction with CAN in MeCN gave rise exclusively to the 5-*endo* product **26**, and no 5-*exo* product was detected, Scheme 8.

In the same way substrate **27** underwent exclusive 5-*endo* cyclization to give **28** in 46% yield. No competing 6-*exo* cyclization or tandem cyclization of the postulated intermediate acyl iminium ion onto the cyclohexenyl group was observed.

In summary, we have demonstrated that efficient 5-*endo* radical−polar crossover reactions can be mediated by CAN in various solvents. The reactions differ from those mediated by $Mn(OAc)_3$ in that products arise from trapping of intermediates by solvent instead of dienes. This may be due to the milder reaction temperatures involved for the CAN-mediated reactions (rt) compared to the $Mn(OAc)_3$ reactions (>70 °C), as the intermediate 5-hydroxylated or 5-alkoxylated products undergo facile elimination of H_2O or ROH upon prolonged heating,[10] or treatment with acid at room temperature. The application of this methodology to the synthesis of the heterocyclic cores of a range of 5,5-*C*,*O*-disubstituted-γ-lactam natural products has been demonstrated.

Acknowledgment. We acknowledge Lilly Research Ltd for a studentship (J.P.M.).

Supporting Information Available: Selected experimental procedures and characterization data for compounds **4**, **8**, **10**, **11**, **17a**, **17b**, **22**, and **27** and representative ^1H and ^{13}C NMR spectra for **9**, **13**, **23**, **24**, and **28**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(10) Compound **4** was observed to eliminate MeOH when heated or treated with p-TSA in toluene at reflux.