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Mn(III) - Promoted Cyclization of Enamides: an Oxidative Radical Approach to β-Lactams

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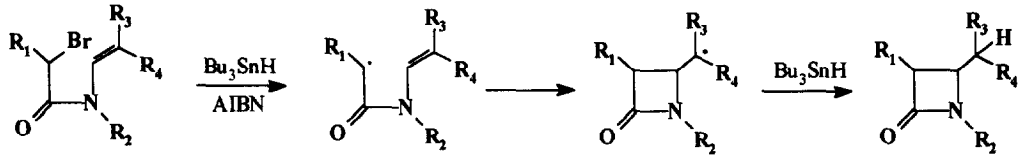
Abstract: α-Carbomethoxy-N-vinylamides were reacted with $Mn(OAc)_3$ in glacial acetic acid at 70°C to afford variously substituted β-lactams in good yields and short reaction times.

In the last years, the synthesis of β-lactams through 4-*exo-trig* cyclization of suitable precursors was extensively studied. Firstly, Pattenden studied the cyclization of N-allylcarbamoylcobalt intermediates to azetidinones under heating or irradiation with a sunlamp.[1a,b] Furthermore, the 4-*exo-trig* cylization of radicals **2**, ganerated by treatmant of α-bromoenamides **1** with Bu_3SnH and AIBN, was contemporarily reported by Belletire[2] and Ishibashi.[3a-e] These reductive methods gave modest to good results, the yields depending mostly on the substituents on the double bond. According to mechanism shown in Scheme 1, the best yields in β-lactams were obtained when R_3 and R_4 were aryl groups or other substituents able to stabilize the radical adduct **3**. The prevalent products obtained by these methods were β-lactams **4**, formed by reduction of **3**.

Scheme 1



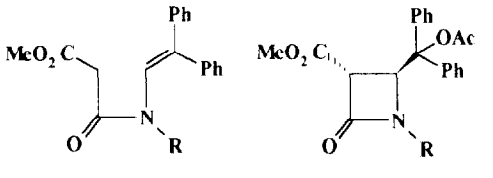
1 2 3 4

On the contrary, intramolecular oxidative radical cyclizations of unsaturated amides had been used to carry out only 5-*exo-trig* and 5-*exo-dig* processes. In this way five-membered lactams and spirolactams were obtained by reaction of N,N-unsaturated dialkyl-β-oxoamides with $Mn(OAc)_3$.[4]

Recently, we have been studying the Mn(III) promoted generation of amidoalkyl radicals from α-oxo or α-cyanoamides, such as malonamide, cyanoacetamide and N-propylcyanoacetamide, and their intermolecular addition to variously substituted alkenes in glacial acetic acid, either under simple mechanical stirring or under ultrasound irradiation. When the reaction was carried out using aryl-substituted olefins, α,β-unsaturated γ-lactones and γ-lactams were obtained, while simple alkyl-substituted olefins gave γ,δ-unsaturated amides.[5,6]

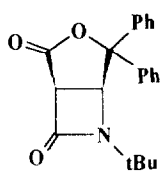
Thus, we continued this work studying the feasibility of Mn(III)-promoted 4-*exo-trig* cyclizations of suitable unsaturated amidic substrates. Our purpose was to estabilish the possible formation, the nature and the stability of the products in these oxidizing conditions, and in this communication we describe our initial results.

The substrates we chose for the start of the work were α-carbomethoxy-N-vinylamides **5**, easily available by literature methods.[7]

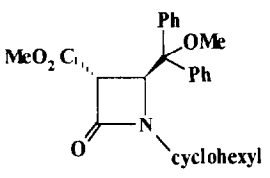


5

9



10

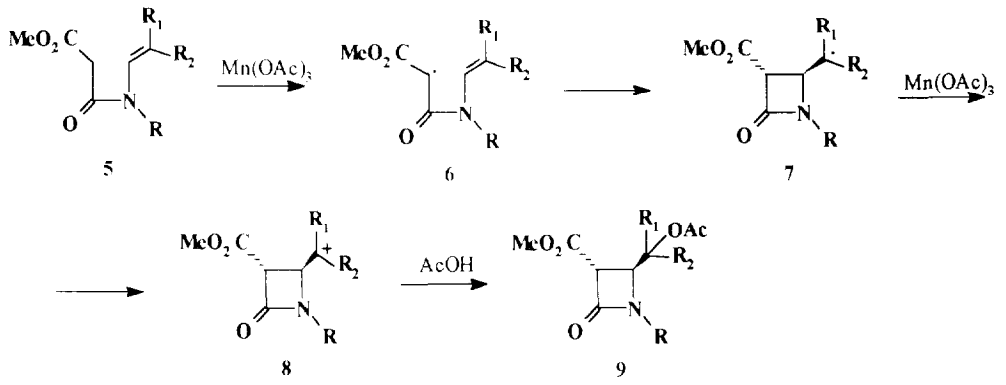


11

5a, 9a R = - Pr
5b, 9b R = - iPr
5c, 9c R = - tBu
5d, 9d R = - Cyclopentyl
5e, 9e R = - Cyclohexyl
5f, 9f R = - CH_2Ph
5g, 9g R = - $CH(CH_3)Ph$

Compounds **5** were reacted in glacial acetic acid with $Mn(OAc)_3$ in a 1:2 molar ratio under simple mechanical stirring at various temperature. The reaction at room temperature did not work well, showing a quite unselective transformation of enamidic substrates into several side-products with very low conversions, even keeping the reaction under stirring for several days. The best results were obtained by heating the reaction mixture at 70°C for few hours; the acetoxylated β-lactams **9** were isolated as the prevalent products in modest to good yields.[8] The probable mechanism of formation of compounds **9** is shown in Scheme 2.

Scheme 2



Results obtained on a series of enamides are shown in Table 1. The highest yields of β-lactams were obtained when both R_1 and R_2 were phenyl groups and this is probably due to the great ability of two aryl groups to stabilize the radical intermediate **7** and to increase the stability of carbocationic intermediate **8** formed by its further oxidation.

As regards the β-lactam stereochemistry, the relative orientation of the substituents on C-3 and C-4 was trans as demonstrated by ^1H-NMR coupling constants of corresponding protons.[9]

Table 1. Reaction of Enamides **5** with $Mn(OAc)_3$ in Acetic Acid

Substrate	Product	Yields[a] (%)	Reaction Time (hr)
5a	**9a**	39	1,5
5b	**9b**	42	"
5c	**9c**	67	"
5d	**9d**	60	"
5e	**9e**	63	"
5f	**9f**	73	"
5g	**9g**[b]	64	"

a) Yields are given on isolated products; b) diastereomeric mixture (1:1 ratio)

In the case of enamide **5c** also compound **10** was obtained in not negligible amounts (y = 19%), showing in its structure a γ-lactonic ring cis-fused with the β-lactamic ring. This products was probably formed by an acid-catalyzed trans-esterification of the corresponding acetoxylated cis β-lactam.

A further confirmation of the mechanism proposed in Scheme 2 was given by the reaction of enamide **5e** with $Mn(OAc)_3$ in MeOH at 70°C. The methoxylated β-lactam **11** (y=26%) was formed together with the acetoxylated compound **9e** (y=32%), according the hypothesis of a cationic intermediate. It is not still clear why in methanol **9e** is formed in the same amount of **11**. A possible explanation could stay in the proximity of manganic acetate to the radical center during the oxidation of adduct **7**, thus, the acetate ligands lost by Mn(III) during its reduction to Mn(II) are allowed to capture intermediate **8**.

Mn(III)-promoted cyclization of phenyl-substituted enamides in acetic acid represents a convenient approach to β-lactams in very simple experimental conditions. β-Lactamic products showed a good stability in acetic acid, even when we let them stay in the reaction mixture for 1-2 days. Moreover, the oxidative mechanism of the reaction seems to allow the cyclization together with the functionalization of the enamidic double bond carbon not involved in the cycle formation. This is a very promising result, because of the possible synthetic applications that could be developed, *e.g.* using Mn(III) complexes with other nucleophilic ligands than acetate in suitable solvents, or carrying out the reaction in presence of different nucleophiles not directly oxidizable by Mn(III). Therefore, our next studies will concern the finding of new experimental conditions in the Mn(III)-promoted synthesis of β-lactams.

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7. Compounds **5** were prepared according the following procedure: diphenylacetaldehyde (5 mmoles) and primary amine (5 mmoles) were stirred in CH_2Cl_2 (40 ml) at room temperature in presence of excess anhydrous $MgSO_4$ for 4-5 hours. $MgSO_4$ was filtered off, and triethylamine (25 mmoles) was added. Then, a solution of monomethyl malonyl chloride (5 mmoles) in CH_2Cl_2 (15 ml) was added dropwise and the reaction mixture stirred for 15 hours. The solvent was removed under reduced pressure to give an oily residue, that was subsequently purified on a silica gel column eluted with petroleum ether/Et_2O to give pure **5** (yields ranges from 20 to 80%).
8. In a typical experimental procedure, enamide **5** (1 mmol) and $Mn(OAc)_3.2H_2O$ (536 mg, 2 mmoles) were added to glacial acetic acid (35 ml) under an argon athmosphere. The suspension was heated at 70°C under stirring for 1.5 hours. Then, water was added (100 ml) and the solution extracted with CH_2Cl_2 (4x25 ml). The organic phase was dried over $MgSO_4$, and the solvent removed under reduced pressure, to give a residue, that was chromatographed on a silica gel column eluted with light petroleum ether/Et_2O to afford pure **9**
9. ^{1}H-NMR spectral data of products (200 MHz, $CDCl_3$); **9a**: 0.87 (3H, t, J = 7.8 Hz, N-C-C-CH_3), 1.56 (2H, se, J = 7.7 Hz, N-C-CH_2-C), 2.14 (3H, s, OAc), 2.81 (1H, dt, J_{AB}= 14.4 Hz, J_2= 7.4 Hz, N-CH_A-C-C), 3.49 (1H, dt, J_{AB}= 14.3 Hz, J_2 = 7.3 Hz, N-CH_B-C-C), 3.68 (1H, d, J =1.9 Hz, H-3), 3.78 (3H, s, COOMe), 5.48 (1H, d, J = 2.3 Hz, H-4), 7.10-7.50 (10H, m, aromatic protons); **9b**: 1.27 (3H, d, J = 6.6 Hz, CH_3), 1.35 (3H, d, J = 6.9 Hz, CH_3), 2.01 (3H, s, OAc), 3.23 (1H, m, **CH**(CH_3)$_2$), 3.67 (1H, d, J = 2.5 Hz, H-3), 3.74 (3H, s, COOMe), 5.41 (1H, d, J = 2.5 Hz, H-4), 7.10-7.50 (10H, aromatic protons); **9c**: 1.22 (9H, s, CH_3), 2.09 (3H, s, OAc), 3.70 (1H, d, J = 2.3 Hz, H-3), 3.75 (3H, s, COOMe), 5.39 (1H, d, J = 2.3 Hz, H-4), 7.1-7.5 (10H, m, aromatic protons); **9d**: 0.85-1.95 (8H, m, cyclopentyl), 2.11 (3H, s, OAc), 3.43 (1H, m, N-CH of cyclopentyl), 3.64 (1H, d, J= 2.4 Hz, H-3), 3.77 (1H, s, COOMe), 5.39 (1H, d, J = 2.4 Hz, H-4), 7.10-7.50 (10H, m, aromatic protons); **9e**: 0.9-2.05 (10H, m, cyclohexyl), 2.12 (3H, s, OAc), 2.74 (1H, m, N-CH of cyclohexyl), 3.68 (1H, d, J = 2.1 Hz, H-3), 3.77 (3H, s, COOMe), 5.40 (1H, d, J = 2.1 Hz, H-4), 7.10-7.50 (10H, m, aromatic protons); **9f**: 2.09 (3H, s, OAc), 3.74 (3H, s, COOMe), 3.85 (1H, d, J_{AB}= 17,4 Hz, CH_A-Ph), 3.92 (1H, d, J = 2.4 Hz, H-3), 4.87 (1H, d, J_{AB}= 17.4 Hz, CH_B-Ph), 5.32 (1H, d, J = 2.4 Hz, H-4), 7.10-7.50 (15H, m, aromatic protons); **9g**: 1.65 (3H, d, J = 7.2 Hz, CH_3), 2.04 and 2.07 (3H, s, OAc), 3.68 and 3.83 (3H, s, COOMe), 3.77 (0.53H, d, J = 2.4 Hz, H-3), 3.87 (0.47H, d, J= 2.6 Hz, H-3), 4.14 and 4.25 (1H, q, J = 7.2 Hz, **CH**(CH_3)Ph), 5.11 (0.47H, d, J = 2.6 Hz, H-4), 5.46 (0.53H, d, J = 2.4 Hz, H-4), 6.85-7.50 (15H, m, aromatic protons); **10**: 0.70-1.10 (9H, s, CH_3 of t-Bu), 3.95 (1H, d, J = 4.8 Hz, H-3), 4.98 (1H, d, J = 4.9 Hz, H-4), 7.10-7.80 (10H, m, aromatic protons); **11**: 0.9-2.1 (10H, m, cyclohexyl), 2.81 (1H, m, N-CH of cyclohexyl), 3.07 (3H, s, OCH_3), 3.63 (1H, d, J = 2.6 Hz, H-3), 3.87 (3H, s, COOMe), 4.89 (1H, d, J 0 2.6 Hz, H-4), 7.10-7.50 (10H, m, aromatic protons).

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