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Manganese(III) Reactions in *N*-Heterocycle Synthesis: The Preparation of Substituted Pyrrolidinones

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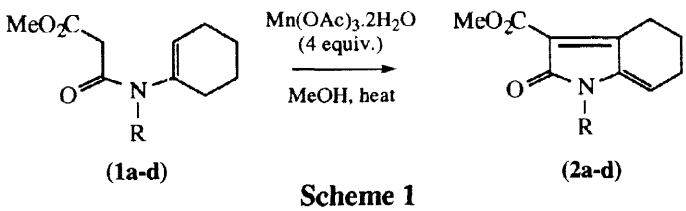
Abstract: The reaction of various *N*-acyl enamines with manganese(III) acetate in boiling methanol has been explored. This was shown to produce functionalised pyrrolidinones *via* a 5-*endo-trig* radical cyclisation.

Keywords: Manganese and compounds; Radicals and radical reactions; Cyclisation; Enamides.

Manganese(III)-based oxidative free-radical cyclisations and annulations have attracted considerable interest in recent years, most notably due to the work of Snider and co-workers.[1] It is clear that this method can offer a number of advantages over alternative methods for mediating free-radical processes *e.g.* using Bu_3SnH or $HSi(SiMe_3)_3$ and AIBN. These include: (i) cost of the reagent; (ii) ease of removal of by-products and (iii) introduction of a functional group (commonly a double bond) after carbon-carbon bond formation. The most commonly used precursors for Mn(III)-based cyclisations have included β-keto esters and malonic esters which readily undergo enolisation. More recently however, the use of less acidic β-amido esters have been explored and these substrates have been shown to cyclise in a 5-*exo*[2] or 4-*exo*[3] manner to give substituted pyrrolidines or β-lactams respectively. The 4-*exo* cyclisation made use of radical stabilising (aromatic) groups on the acceptor double bond of the *N*-acyl enamine precursor. These previous studies prompted us to explore the cyclisation of *N*-acyl enamines leading to the formation of substituted pyrrolidinones *via* a 5-*endo-trig* cyclisation reaction. Previous work had shown that Bu_3SnH[4] or Ni/AcOH[5] could be used to effect this unusual (disfavoured) cyclisation process but the use of Mn(III) has not been previously reported.



(1a-d) **(2a-d)**

Scheme 1

Entry	1	R	Yield of 2 (%)
1	a	Bn	38(22*)
2	b	Bu	52
3	c	PMB	39
4	d	PFB#	35

*Using 2 equiv. of $Mn(OAc)_3$. #PFB = *p*-fluorobenzyl.

Table

Initial studies concentrated on the synthesis and subsequent cyclisation of *N*-acyl enamines (**1a-d**) (Scheme 1). These were readily prepared (in 41-61% yield) on heating cyclohexanone with the appropriate amine followed by acylation of the resultant imine using methyl malonyl chloride. Reaction of (**1a**) with 2

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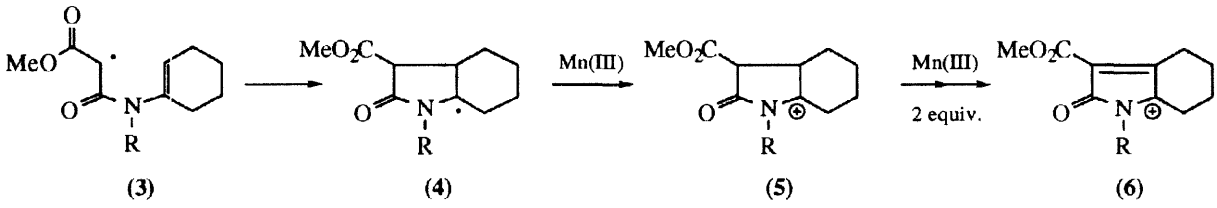
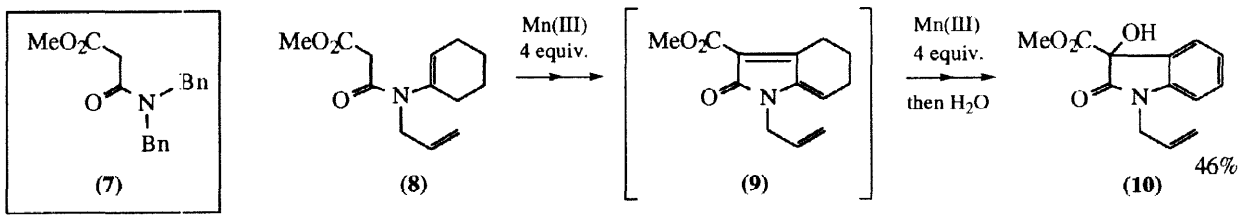
equivalents of $Mn(OAc)_3$ in boiling methanol resulted in the disappearance of starting material and diene **(2a)** was isolated in only 22% yield after column chromatography (Table, entry 1). Attempts to improve this yield by addition of $Cu(OAc)_2.H_2O$ and/or using AcOH as the solvent failed.[6] However, the yield of **(2a)** could be improved to 38% when 4 equivalents of $Mn(OAc)_3$ (added in one portion) were employed. This was the optimum yield and the addition of further equivalents of $Mn(OAc)_3$ was found to have a detrimental effect. Reaction of related amides **(1b-d)**, under the same conditions, gave rise to dienes **(2b-d)** in similar yields (Table, entries 2-4).[7]



(3) (4) (5) (6)

Scheme 2

The mechanism of these reactions may involve 5-*endo* cyclisation of carbamoylmethyl radical **(3)** to form tertiary radical **(4)** (Scheme 2). The initial radical **(3)** could be generated from an intermediate Mn(III) enolate produced on reaction of **(1a-d)** with Mn(III). Subsequent oxidation of **(4)**, by a second equivalent of Mn(III), to produce **(5)** followed by loss of a proton and further radical generation/oxidation could give rise to cation **(6)**. Final deprotonation produces diene **(2)** and the entire sequence requires 4 equivalents of Mn(III) which is consistent with the experimental results described earlier. Radical **(3)**, derived from *N*-benzyl precursors **(1a)** and **(1c-d)**, could also undergo a competitive oxidative cyclisation by reaction with the aromatic ring. However, this was thought to be unlikely as treatment of the dibenzylamide **(7)** with Mn(III) yielded only recovered starting material (in 86% yield after column chromatography).

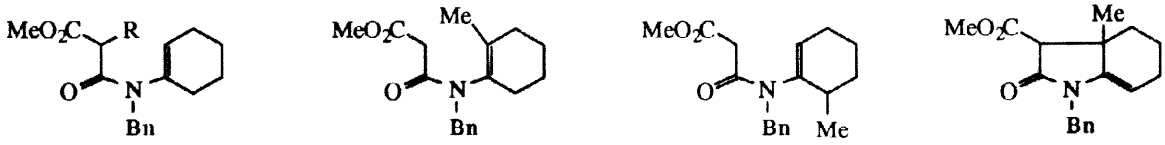


(7) (8) (9) (10)

Scheme 3

An unexpected result was obtained on reaction of the *N*-allyl derivative **(8)** which has the potential to undergo 5-*endo* or 5-*exo* cyclisation by reaction with the *N*-allyl double bond (Scheme 3). In this case, reaction of **(8)** with 4 equivalents of Mn(III) produced the oxindole **(10)** in 17% yield. This could be improved to 46% yield by the portionwise addition of 8 equivalents of Mn(III) to **(8)** over 8 h. The mechanism for this reaction may well involve the intermediacy of diene **(9)** which could then be oxidised further to the aromatic **(10)**. It is not clear as to why the introduction of an *N*-allyl group leads to further oxidation. Indeed, the diene **(9)** was not even isolated when using 2 equivalents of Mn(III), only **(10)** was present in 24% yield.

These results prompted us to explore the reaction of α-substituted β-amido esters **(11a)** and **(11b)**. After initial 5-*endo* cyclisation the pyrrolidinone product would have no acidic α-hydrogens and therefore cannot undergo further oxidation (to *e.g.* a diene). However, reaction of **(11a)** or **(11b)** with Mn(III) (4 equivalents) in boiling methanol only gave rise to recovered starting material in 89 and 92% yield respectively.



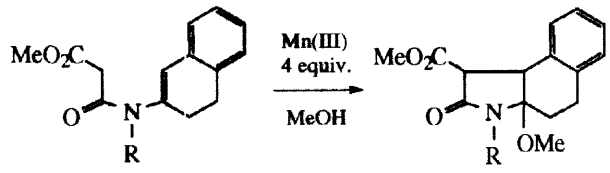
(11a) R=Cl
(11b) R=Me

(12)

(13)

(14)

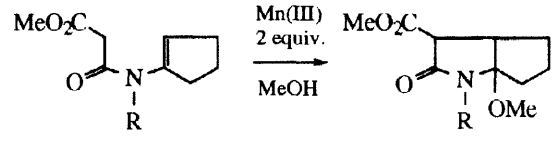
The cyclisation of an inseparable mixture of 2- and 6-methylcyclohexenyl precursors, **(12)** and **(13)**, in a ratio of 1:1.5 was then investigated. Reaction with 4 equivalents of Mn(III) resulted in the isolation of alkene **(14)** in 44% yield. This was presumably derived from **(12)** and no product resulting from the cyclisation of **(13)** was recovered which may be due to prior acid-catalysed isomerisation of **(13)** to **(12)** under the reaction conditions.[8]



(15) R=Bn
(16) R=Bu

(17) R=Bn, 26%
(18) R=Bu, 23%

Scheme 4

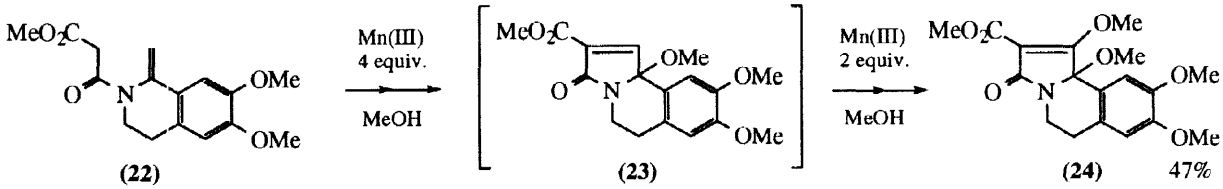


(19) R=Bn
(20) R=allyl

(21) R=Bn, 39%

Scheme 5

The Mn(III) promoted cyclisation of β-tetralone-derived precursors **(15)** and **(16)** followed an alternative pathway (Scheme 4). In this case, cyclisation to produce a cation of type **(5)** (Scheme 2) was followed by nucleophilic addition of methanol (rather than deprotonation) to give the methoxy derivatives **(17)**-**(18)** (as single diastereoisomers). The alternative fate of the cation may be a consequence of ring strain and a similar product was isolated from the cyclopentanone derivative **(19)** (Scheme 5). Once again nucleophilic trapping of the intermediate cation rather than deprotonation to form a ring strained alkene or diene was observed. When 4 equivalents of Mn(III) were used the yield of **(21)** was 21% but this could be improved to 39% by the portionwise addition of 2 equivalents of Mn(III) over 8 h. This can be compared with reaction of the *N*-allyl derivative **(20)** with Mn(III) (2 or 4 equivalents) or Mn(III)/Cu(II) (2:1 equivalents) where no cyclisation products were isolated.



(22)

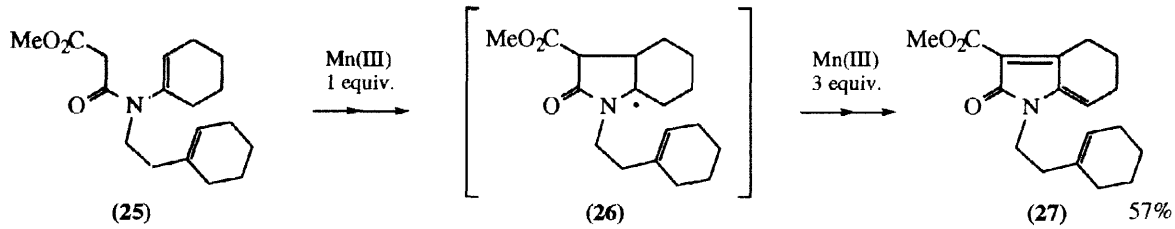
(23)

(24) 47%

Scheme 6

The effect of the C=C double bond substitution was also investigated by cyclisation of bicyclic enamine **(22)** using 6 equivalents of Mn(III) and this gave rise to yet another class of compound, namely enol ether **(24)** (Scheme 6). The formation of **(24)** could involve Michael-type addition of MeOH[9] to intermediate **(23)** [itself derived from reaction of MeOH with a benzylic cation of type **(6)** (Scheme 2)] followed by further Mn(III)-promoted oxidation to introduce the double bond. Repeating the reaction using 2 or 4 equivalents of Mn(III) still gave rise to **(24)** but in lower yield (28 or 31% respectively).

Finally, with a view to intercepting the intermediate radical or cation involved in these cyclisation reactions, the *N*-cyclohexenylethyl precursor (**25**) was prepared (Scheme 7). On treatment with Mn(III) the pyrrolidinone radical (**26**) was expected and this could undergo 5-*exo* or more likely 6-*endo* intramolecular cyclisation by reaction with the trisubstituted double bond. However, only diene (**27**) was isolated and thus the rate of oxidation of radical (**26**) [to an *N*-acyliminium ion of type (**5**) (Scheme 2)] is faster than the intramolecular radical cyclisation. In addition, the resulting *N*-acyliminium ion prefers to undergo deprotonation rather than cyclisation by reaction with the electron-rich double bond (which is contrary to that observed in related systems[10]).



(**25**) (**26**) (**27**) 57%

Scheme 7

This work has demonstrated the novel application of Mn(III) promoted *N*-acyl enamine cyclisations in pyrrolidinone synthesis. The reaction provides a quick, easy and mild approach to a variety of functionalised *N*-heterocycles in a one-pot reaction. Further studies directed towards the synthesis of alkaloids (and related compounds) using this method are currently underway.

Typical Procedure

To a stirred solution of the enamine (0.34-0.79 mmol) in MeOH (25-35 cm^3) under nitrogen was added a suspension of $Mn(OAc)_3$. $2H_2O$ (1.34-3.16 mmol) in MeOH (10-15 cm^3) and the mixture was heated at reflux for 12 h until all the starting material had been consumed as indicated by TLC. The solvent was removed *in vacuo* and the residue dissolved in EtOAc (15 cm^3) and water (15 cm^3). The organic layer was separated, washed with water, brine, dried ($MgSO_4$) and then evaporated *in vacuo* to afford crude product which was purified by column chromatography (silica).

Acknowledgements

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References and Notes

1. Snider, B.B. *Chem. Rev.*, **1996**, *96*, 339-363.
2. (a) Galeazzi, R.; Mobbili, G.; Orena, M. *Tetrahedron*, **1996**, *52*, 1069-1084. (b) Cardillo, B.; Galeazzi, R.; Mobbili, G.; Orena, M. *Synlett*, **1995**, 1159-1160.
3. D'Annibale, A.; Resta, S.; Trogolo, C. *Tetrahedron Lett.*, **1995**, *36*, 9039-9042.
4. (a) Goodall, K.; Parsons, A.F. *Tetrahedron*, **1996**, *52*, 6739-6758. (b) Sato, T.; Nakamura, N.; Ikeda, K.; Okada, M.; Ishibashi, H.; Ikeda, M. *J. Chem. Soc., Perkin Trans. 1*, **1992**, 2399-2407. (c) Ishibashi, H.; Higuchi, M.; Ohba, M.; Ikeda, M. *Tetrahedron Lett.*, **1998**, *39*, 75-78.
5. Cassayre, J.; Quiclet-Sire, B.; Saunier, J-B.; Zard, S.Z. *Tetrahedron*, **1998**, *54*, 1029-1040.
6. Copper(II) acetate is often employed as a co-oxidant in manganese(III)-mediated reactions (see ref. 1).
7. All new compounds exhibited satisfactory spectral and analytical (high resolution mass) data.
8. The ratio of (**12**):(**13**) could be altered by heating the mixture in methanol containing acetic acid. After 8 h, the ratio was seen (from the ^1H NMR spectrum) to change from 1:1.5 to 1.2:1.
9. Delépine, J-L.; Pecquet, P.; Betton, M-c.; Huet, F. *Synth. Commun.*, **1996**, *26*, 2819-2829.
10. For related *N*-acyliminium ion cyclisations see (a) Speckamp, W.N.; Hiemstra, H. *Tetrahedron*, **1985**, *41*, 4367-4416. (b) Choi, J-K.; Jung, Y-S.; Park, N-S. *Bull. Korean Chem. Soc.*, **1988**, *9*, 129-132.