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Manganese(III)-mediated radical cyclisations for the (*Z*)-selective synthesis of *exo*-alkylidene pyrrolidinones and pyrrolidines†

Harriet A. Keane, Wilfried Hess and Jonathan W. Burton*

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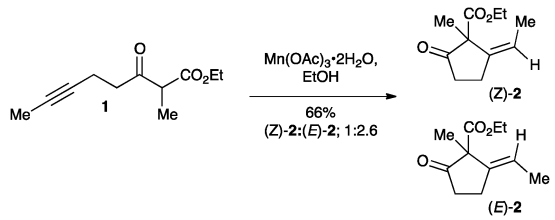
The cyclisation of alkynyl amido- and amino-malonates in the presence of manganese(III) acetate gives *exo*-alkylidene pyrrolidinones and pyrrolidines with a preference for the (*Z*)-alkene product isomer.

Pyrrolidines and pyrrolidinones are important heterocyclic structural motifs that are present in many ligands, are used in the field of organocatalysis and found in a wide variety of natural products. Inspired by the indium(III)-catalysed Conia-ene reaction of alkynyl α-aminomalonates described by Hatakeyama[1] and co-workers, we recently reported the use of zinc(II) halides for the *exo* (and *endo*) cyclisation of alkynyl α-aminomalonates to give (*E*)-alkylidene pyrrolidines and pyrrolidinones with high selectivity.[2–4] Herein we describe a complementary method for the synthesis of (*Z*)-alkylidene pyrrolidinones and pyrrolidines from alkynyl α-aminomalonates.

We,[5] and others,[6,7] have shown that alkenyl malonates can be converted into cyclopentanes and [3.3.0]-bicyclic γ-lactones on exposure to manganese(III) acetate[8] and an appropriate copper(II) salt[9] and we have applied this oxidative radical methodology in the total synthesis of a cyclopentane-containing natural product.[10] With acetylenic substrates, however, reduction of the vinylic adduct radical tends to occur by H-atom abstraction from solvent.[7] Snider has previously shown that exposure of the alkynyl acetoacetate **1** to manganese(III) acetate in ethanol gives rise to the alkylidene cyclopentanones **2** in 66% yield with modest (*E*)-selectivity (Scheme 1).[7]



Scheme 1 Cyclisation of alkynyl acetoacetate **1** reported by Snider.[7]

Department of Chemistry, University of Oxford, Chemistry Research Laboratory, 12 Mansfield Road, Oxford, OX1 3TA, UK. E-mail: jonathan.burton@chem.ox.ac.uk; Fax: +44 (0)1865 285002
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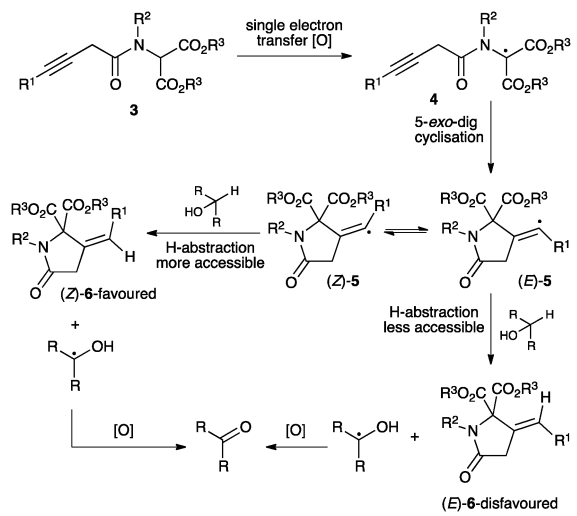
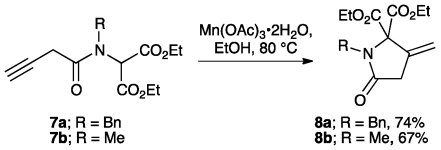
Based on this precedent, we proposed that cyclisation of an appropriately substituted malonyl radical **4** derived from **3**, onto an alkyne would deliver the corresponding alkenyl radical **5** which would likely exist as an equilibrating mixture of (*E*) and (*Z*)-isomers (Scheme 2).[11] We surmised that using a suitably bulky alcohol might result in H-atom abstraction occurring more readily from the (*Z*)-adduct radical, (*Z*)-**5**, to give the (*Z*)-alkylidene pyrrolidinone, (*Z*)-**6**, selectively giving a complementary methodology to our zinc(II) and Hatakeyama's indium(III)-catalysed methodology for the formation of (*E*)-alkylidene pyrrolidines/pyrrolidinones.[12]

As a starting point, we investigated the cyclisation of the terminal alkyne substrates **7**.[13] Exposure of the amidomalonates **7a**[14] and **7b** to manganese(III) acetate in ethanol at reflux[6,7,12] delivered the corresponding *exo*-methylene pyrrolidinones **8a** and **8b** in 67% and 74% yield respectively (Scheme 3). Encouragingly, no trace of product arising from 6-*endo*-dig

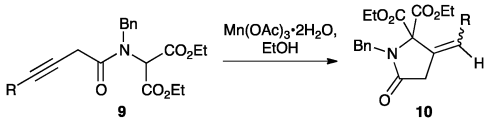


Scheme 2 Mechanistic hypothesis for formation of (*Z*)-alkylidene pyrrolidinones.



Scheme 3 Cyclisation of terminal acetylene substrates.

Table 1 Cyclisation of internal alkyne substrates[16]



Entry	*R*	*T*	Time	Product	Yield (%)	*E*/*Z*
1	Me	80 °C	15 h	**10a**	78	1 : 3.8
2	Me	RT	15 min	**10a**	75	1 : 3.9
3[a]	Me	80 °C	15 h	**10a**	68	1 : 1.8
4	Et	RT	2 h	**10b**	86	1 : 4.7
5	*n*Pr	RT	2 h	**10c**	72	1 : 2.9
6	*n*Bu	80 °C	15 h	**10d**	73	1 : 3.0
7	Ph	RT	2 h	**10e**	65	1 : 3.0

[a] Reaction was conducted in acetonitrile.

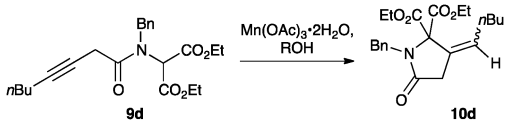
cyclisation was detected in the crude ^{1}H NMR spectrum neither was there any trace of the thermodynamically more favoured α,β-unsaturated γ-lactams derived from conjugation of the olefinic double bond in **8**. Given this encouraging initial result we moved to examine the cyclisation of internal alkyne substrates **9** (Table 1).

Cyclisation of the internal alkyne **9a** at 80 °C in ethanol gave the *exo*-alkylidene pyrrolidinone **10a** in 78% yield as a 1 : 3.8 mixture of alkene isomers pleasingly with the (*Z*)-geometrical isomer predominating[15] and in contrast to the cyclisation of **1** reported by Snider.[7] We found that these cyclisations could be conducted at room temperature in 2 h or less (Table 1, entries 2, 4, 5 and 7). The geometrical integrity of the (*Z*)-alkene **10d** was preserved on re-exposure to the reaction conditions indicating that the product diastereocontrol is likely the result of kinetically controlled hydrogen abstraction by the equilibrating adduct radicals **5**. The use of acetonitrile resulted in the product being isolated with similar yield but with reduced diastereocontrol (Table 1, entry 3). The ethyl, propyl and butyl-substituted alkynes behaved similarly to the methyl substituted alkyne **9a** giving the corresponding *exo*-alkylidene pyrrolidinones in 72–86% yield and up to 4.7 : 1 (*Z*) : (*E*)-selectivity (Table 1, entries 4–6). The phenylacetylene **9e** also underwent cyclisation to give the corresponding *exo*-arylidene pyrrolidinone **10e** in 65% yield and 3 : 1 (*Z*) : (*E*)-selectivity (Table 1, entry 7).

The results reported in Table 1 were encouraging in that the pyrrolidinones **10** were formed in synthetically useful yields with moderate diastereocontrol. We therefore decided to investigate the influence of different alcohols as hydrogen atom donors. With the butyl-substituted alkyne **9d**, moving from ethanol to *n*-pentanol (PentOH) resulted in the product **10d** being isolated in 78% yield with the same selectivity (*Z*)-selectivity (Table 2, entries 1 and 2). Moving to a considerably more hindered alcohol, *iso*-propanol, resulted in full conversion with formation of the product **10d** in 75% yield but with improved (*Z*)-selectivity (Table 2, entry 3). The use of benzyl alcohol as solvent resulted in the product being formed in 85% yield but with reduced (*Z*)-selectivity (Table 2, entry 4). Using *iso*-propanol as solvent, and reducing the reaction temperature resulted in the product **10d** being formed with improved (*Z*)-selectivity albeit in reduced yield (Table 2, entry 6).[17]

Unfortunately, using the same conditions with the phenyl-substituted acetylene **9e** (*iso*-propanol, 20 °C) resulted in the

Table 2 Screening of various alcohols as H-atom donors[16]



Entry	Solvent	*T*/°C	*t* (h)	Yield (%)	*E*/*Z*
1	EtOH	80	15	73	1 : 3.0
2	PentOH	80	15	78	1 : 3.0
3	*i*PrOH	80	15	75	1 : 4.5
4	BnOH	80	15	85	1 : 2.0
5	EtOH	20	2	78	1 : 3.0
6	*i*PrOH	20	3	51	1 : 6.0

product being formed with only approximately 1 : 3 (*E*) : (*Z*) selectivity along with numerous by-products.[17] In terms of substrate generality and maximising the yield of (*Z*)-*exo*-alkylidene pyrrolidinones, ethanol is the best initial solvent choice for these reactions with subsequent substrate-specific solvent optimisation potentially allowing improved (*Z*)-selectivity.

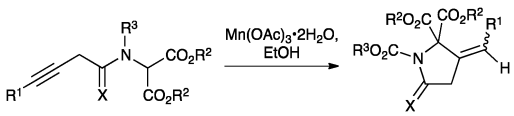
Using ethanol as the solvent, we next briefly investigated the substrate scope for the formation of pyrrolidines and pyrrolidinones (Table 3). It was anticipated that increasing the bulk of the esters should lead to higher amounts of the (*Z*)-*exo*-alkylidene pyrrolidinone. We compared the cyclisations of the diethyl (**9d**), dibenzyl (**11**) and di*t*-butyl (**13**) malonates (Table 3, entries 1–3). As expected, increasing the size of the malonic esters gave the product *exo*-alkylidene pyrrolidines with increased (*Z*)-selectivity (Table 3, entries 1–3).

We also investigated the synthesis of pyrrolidines by the cyclisation of *N*-carbamoyl-protected alkynyl malonates **15** (Table 3, entries 4–6).[13] These substrates **15** underwent cyclisation under our standard reaction conditions to give the corresponding alkylidene pyrrolidines **16** in 69–78% yield. The internal alkyne **15c** gave the product **16c** with 2.8 : 1 (*Z*) : (*E*) selectivity.

Not only are these cyclisations applicable to the formation of 5-membered rings but it is also possible to synthesise piperidinones. Thus, exposure of the alkynyl malonates **17a** and **17b** to manganese(III) acetate in ethanol at 80 °C gave the corresponding piperidinones **18a** and **18b** in 66% and 71% yields respectively (Scheme 4).[16]

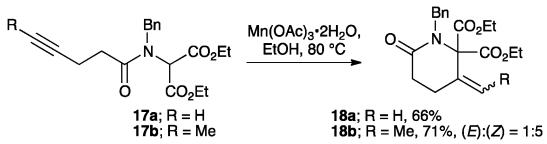
In conclusion we have developed a mild and efficient manganese(III)-mediated cyclisation reaction of alkynoic amidomalonates and protected aminomalonates. This provides

Table 3 Substrate scope[16,18]



Entry	R^1	R^2	R^3	Substrate	Product	Yield (%)	*E*/*Z*
1[a]	*n*Bu	Et	Bn	**9d**, X = O	**10d**	73	1 : 3.0
2[b]	*n*Bu	Bn	Bn	**11**, X = O	**12**	79	1 : 3.5
3[a]	*n*Bu	*t*Bu	Bn	**13**, X = O	**14**	82	1 : 6.6
4[a]	H	Et	CO_2Bn	**15a**, X = H_2	**16a**	78	—
5[b]	H	*t*Bu	CO_2Et	**15b**, X = H_2	**16b**	78	—
6[b]	*n*Bu	Et	CO_2Et	**15c**, X = H_2	**16c**	69	1 : 2.8

[a] Reaction was conducted at 80 °C. [b] Reaction was conducted at RT.



Scheme 4 Synthesis of *exo*-alkylidene piperidinones.

a convenient and practical entry into the synthesis of (*Z*)-*exo*-alkylidene pyrrolidinones and pyrrolidines respectively. The products can be obtained in good yields with a clear preference for the sterically more demanding (*Z*)-products, rendering the approach complementary to previously developed Conia-ene type reactions.[1,2]

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12 For previous work on the synthesis of *exo*-methylene pyrrolidinones by manganese(III)-mediated cyclisation of appropriately substituted β-keto carboxamides see: ref. 4*a*,*e*.
13 The amidomalonates were readily prepared according to the method of Hatakeyama see ref. 1.
14 The amidomalonate **7a** undergoes cyclisation on exposure to mildly acidic conditions during silica gel chromatography. Cyclisation of the *N*-PMB dimethyl malonate analogue of **7a** under indium(III) catalysis has previously been reported by Hatakeyama. Additionally cyclisation of a closely related amidomalonate on silica gel has also been observed by Hatakeyama, see ref. 1.
15 Cyclisation of **9a** under zinc(II) catalysis gives **10a** with high (*E*)-selectivity see ref. 2. Hatakeyama has reported cyclisation of a closely related substrate under indium(III) catalysis see ref. 1.
16 The stereochemistry of the products was assigned on the basis of ^{1}H NMR NOE experiments. The (*E*) : (*Z*) ratios were measured by ^{1}H NMR.
17 The reactions conducted in *iso*-propanol at room temperature resulted in complete conversion, however, numerous by-products were also formed.
18 The stereochemistry of **12** and **14** was assigned by NMR comparison with the other products reported in the paper.

