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Intramolecular amidocyclopropanation reactions using diethoxymethyl-functionalised lactams as organozinc carbenoid precursors

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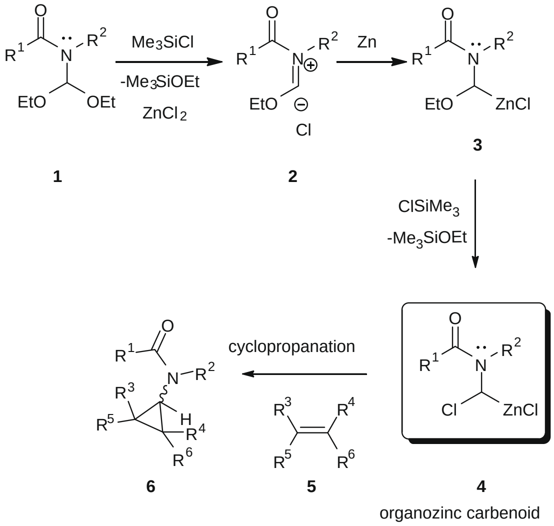
ABSTRACT

Intramolecular amidocyclopropanation reactions of diethoxymethyl-lactams containing a pendant alkene were examined using zinc/TMSCl. With a range of 4–6-membered lactams, bicyclic amidocyclopropanes were obtained with very high diastereoselectivity with a preference for the formation of the more hindered *endo*-cyclopropane.

The aminocyclopropyl unit is present in a considerable number of biologically active natural products and pharmaceuticals.[1] In structural terms, the rigidity of this small ring provides an excellent molecular scaffold for precise location of functional groups within a more complex system. In contrast to traditional carbene or carbenoid methods for aminocyclopropane synthesis such as Simmons-Smith addition to an enamine or enamide derivative[2] or those that require subsequent functional group manipulation, as in the Curtius rearrangement of cyclopropyl carboxylic acids,[3] our current strategy involves direct cyclopropanation of simple alkenes using heteroatom-functionalised organozinc carbenoids.[4–6] Thus, as encapsulated in Scheme 1, an organozinc carbenoid **4** can be generated directly and efficiently from a diethoxymethylamide **1** in the presence of metallic zinc, chlorotrimethylsilane and a Lewis acid. A plausible mechanism involves activation of an ethoxy group of the orthoamide by the Lewis Acid and chlorotrimethylsilane, thus generating an intermediate **2**, which, on subsequent delivery of two electrons from zinc leads to the organozinc carbenoid **4** which can then cyclopropanate an alkene (Scheme 1).

We have recently reported on the use of this protocol for the synthesis of a variety of structurally interesting functionalised amidocyclopropanes[6] and, in view of the significant number of antiviral,[7] antibacterial[8] and antitumour compounds[9] that contain an aminocyclopropyl ring within a polycyclic framework, it was of particular interest to investigate the potential of the intramolecular variant of our organozinc carbenoid reaction on suitably substituted lactams **7-12** (Scheme 2).



Scheme 1.

In recent times, a variety of approaches for the preparation of polycyclic aminocyclopropanes via intramolecular reactions have been reported, including elegant variants of the Kulinkovich[10] reaction developed by de Meijere[11] using Ti(II)-mediated coupling of tethered *N*,*N*-dialkylamides,[12] and transition metal-mediated

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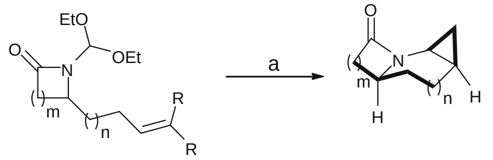


7 m=1, n=1, R =H
8 m=2, n=1, R =H
9 m=2, n=2, R =H
10 m=3, n=1, R =H
11 m=3, n=2, R =H
12 m=2, n=1, R =Me

13 m=1, n=1
14 m=2, n=1
15 m=2, n=2
16 m=3, n=1
17 m=3, n=2

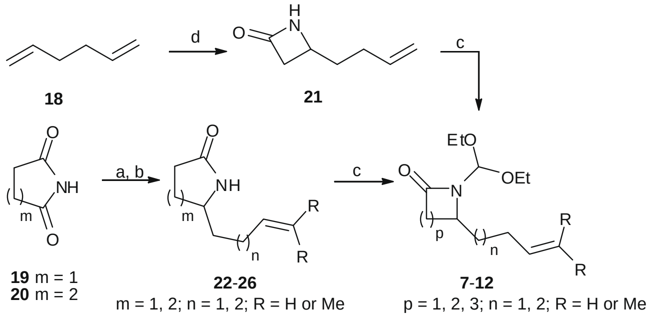
Scheme 2. Reagents and conditions: (a) Zn source, Me_3SiCl, $ZnCl_2$, Et_2O, 44 °C.

cyclopropanation of enamides with diazoesters.[13] It should be noted however, as highlighted in Scheme 2, that the tricyclic products produced in the present method also contain a lactam functionality which is useful for further elaboration, and that, in contrast to the titanium-mediated intramolecular cyclopropanation of ω-vinylimides,[12a] a linearly fused tricyclic system is obtained.

The lactams **22**–**26** were prepared simply from cyclic imides **19** and **20** by a one-pot sequence involving reaction with an excess of the appropriate unsaturated Grignard reagent, followed by reduction,[14] whilst lactam **21** was prepared by [2+2] cycloaddition of 1,5-hexadiene **18** and chlorosulfonyl isocyanate (Scheme 3).[15] The lactams were then heated in triethyl orthoformate at 160 °C in the presence of a catalytic amount of aluminium chloride to give the diethoxymethyl-lactams **7**–**12**.[16] The yields for these steps are given in Table 1.

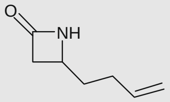
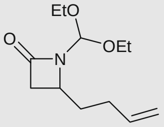
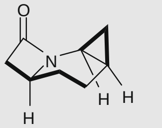
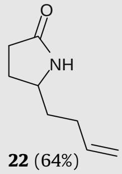
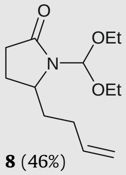
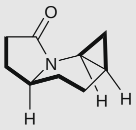
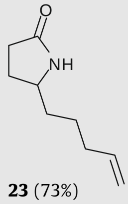
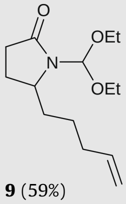
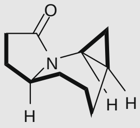
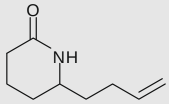
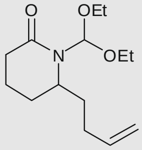
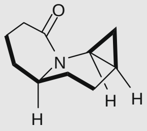
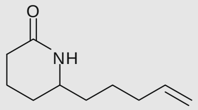
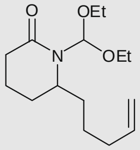
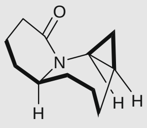
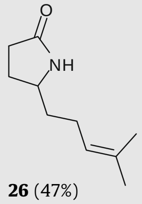
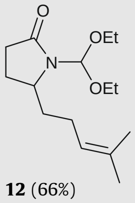
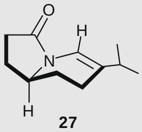
With the carbenoid precursors **7**–**12** in hand, the intramolecular cyclopropanation was readily performed using a zinc source in the presence of trimethylsilyl chloride and zinc chloride in refluxing diethyl ether, to give the corresponding cyclopropanes in moderate yields (Scheme 2, Table 1). Trace amounts of the starting lactam derived from hydrolysis of the orthoamide were also noted.

Examination of these results reveals that selection of a tethered γ-lactam derivative provided the highest yields (entries 2 and 3) irrespective of whether the organozinc carbenoid was participating in formation of a bicyclo [4.1.0] (six-membered ring) or a [5.1.0] (seven-membered ring) subunit. By way of contrast, the use of either the more conformationally mobile tethered δ-lactams (entries 4 and 5) or the relatively rigid β-lactam (entry 1) led to a significant reduction in yield. Moreover, the selection of a trisubstituted alkene tether as in substrate **12** (entry 6) furnished a mixture of the cyclic alkenes **27** and **28**, as evidenced by NMR analysis of the crude reaction mixture, and no cyclopropane was detected. A possible mechanism for the formation of **27** and **28** is outlined in Scheme 4.



Scheme 3. Reagents and conditions: (a) $R_2C{=}CH(CH_2)_nCH_2MgBr$, THF; (b) $NaBH_3CN$, AcOH, THF, then 5% aq NaOH; (c) $AlCl_3$, $CH(OEt)_3$, 160 °C; d) $ClSO_2NCO$, CH_2Cl_2, rt, 7 d, then Na_2SO_3, KOH, H_2O.

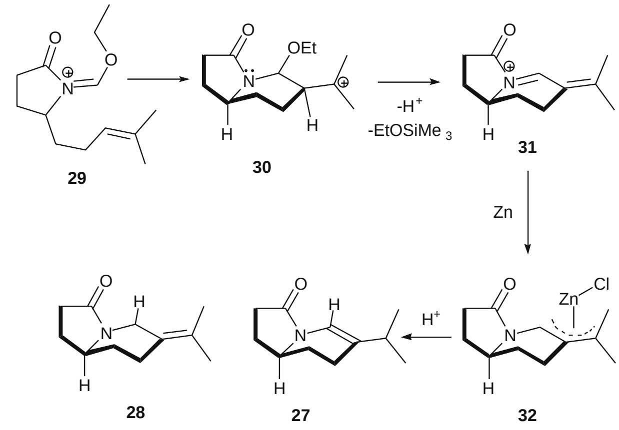
Table 1

Entry	Amide (yield)	Orthoamide (yield)	Cyclopropane (yield)
1	 **21** (37%)	 **7** (32%)	 **13** (21%)[c]
2	 **22** (64%)	 **8** (46%)	 **14** (41%)[a]
3	 **23** (73%)	 **9** (59%)	 **15** (41%)[b]
4	 **24** (66%)	 **10** (42%)	 **16** (21%)[c]
5	 **25** (68%)	 **11** (55%)	 **17** (26%)[c]
6	 **26** (47%)	 **12** (66%)	 **27** Not isolated[a]

[a] Zn(Hg).
[b] Zn.
[c] Zn/CuCl.

Clearly, in this instance, cyclisation of the trisubstituted alkene onto the low energy *N*-acyl iminium cation **29** must be faster than two-electron reduction by zinc. Proton loss followed by Lewis acid mediated departure of the second ethoxy group then gives the conjugated acyl iminium ion **31**, which can be reduced to give the allylzinc species **32**. Protonation of **32** then gives a mixture of the two alkenes **27** and **28**.

From a stereochemical standpoint, it was important to determine whether the cyclopropane unit was the more hindered *endo*



Scheme 4.

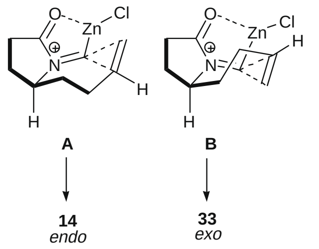


Figure 1.

isomer **14**, as opposed to the sterically less congested *exo* diastereoisomer **33** (Table 2). Since these two isomers were not likely to be distinguishable using simple NMR techniques, a combined NMR calculation and molecular modelling approach was used to determine which structural isomer provided the best fit with the NMR data.

Thus, the geometry of the predominant configuration and conformation for each polycylic compound was confirmed by a detailed comparison of the observed ^{1}H–^{1}H coupling constants and nuclear Overhauser enhancements (NOE) with values obtained from molecular mechanics calculations using the MMX force field[18] followed by DFT calculations using the B3LYP/6-31G(d) level of theory.[19] As an illustration, in the case of compounds **14** and **33** computational studies allowed prediction of the NOE ratios, dihedral angles, chemical shifts and coupling constants for both isomers as depicted in Table 2, showing two large $^3J_{HH}$ couplings on proton 3a-H. Comparison with the experimental results clearly indicated the *endo*-orientation of the 3-CH$_2$ and the cyclopropane ring (denoted as *endo*-C$_1$,C$_3$). In particular, on selective excitation of proton 1′-H the corresponding enhancement ratio for protons 3-H and 2’-H ($\eta_{1' \to 3}/\eta_{1' \to 2'}$) was found to be 3.4. From the B3LYP/6-31G(d)-optimised geometry, it can be noticed that the internuclear distances, *r*, between protons 1′-3 and 1′-2′ in the *endo*-C$_1$,C$_3$ conformation are 2.44 Å and 3.09 Å, respectively. Thus, using the initial rate approximation,[20] which is based on the r^{-6} dependence of NOEs, the expected enhancement ratio is 4.1. This compares well with the measured value of 3.4. For comparison, the expected NOE ratio is only 0.1 in the alternative *exo*-C$_1$,C$_3$ conformation (Table 2). A detailed discussion of this approach and further examples are provided in supplementary data.

The preference for formation of the more hindered product may possibly be rationalised by consideration of the two possible transition states shown in Figure 1, both of which feature an ‘amidoorganozinc carbenoid’ in which the oxygen atom of the lactam is coordinated to the zinc atom. The observed stereochemical outcome would result from the less strained and less sterically congested approach of the alkene to the carbenoid **A**, rather than the somewhat more hindered approach **B** which would lead to the *exo* isomer.

In summary, the results of this preliminary study clearly demonstrate that amidoorganozinc carbenoids derived from suitably constituted *N*-diethoxymethyl-lactams can successfully participate in intramolecular reactions with tethered monosubstituted alkenes. In all cases studied, only one diastereoisomer was isolated and the stereochemical preference is for formation of the cyclopropane on the more hindered concave face of the molecule. From an experimental standpoint, it can be seen that the overall sequence is inexpensive and the zinc/chlorotrimethylsilane-mediated cyclopropanation reaction occurs under mild conditions, thus paving the way for the construction of a range of usefully functionalised polycyclic amidocyclopropane systems.

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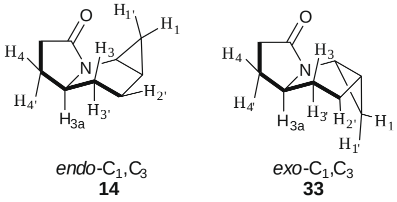
Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2009.03.224.

Table 2

Vicinal $^3J_{HH}$ couplings were predicted using a Karplus-type equation,[17] accounting for the dependence of $^3J_{HH}$ on both the dihedral angle and the substituent electronegativities



	NOE ratio	Dihedral angles (°)		Coupling constants (Hz)	
	$\eta_{1' \to 3}/\eta_{1' \to 2'}$	H^{3}CCH^{3a}	H^{3a}CCH^4	$J_{3,3a}$	$J_{3a,4}$
Predicted for **14**	4.1	177	154	11.8 (9.6)	10.3 (8.2)
Predicted for **33**	0.1	177	153	11.8 (9.6)	10.2 (7.9)
Observed	3.4			11.5	8.8

The values shown in brackets are from the B3LYP/6-311+G(2d,p) calculations of the *J* couplings.

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