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The generation and trapping of organozinc carbenoids from *N*-diethoxymethyl amides: a new amidocyclopropanation reaction

Guillaume Bégis,[a] David Cladingboel[b] and William B. Motherwell*[a]

[a] *Department of Chemistry, Christopher Ingold Laboratories, University College London, 20 Gordon Street, London, UK WC1H 0AJ. E-mail: w.b.motherwell@ucl.ac.uk*

[b] *AstraZeneca R&D Charnwood, Bakewell Road, Loughborough, UK LE11 5RH*

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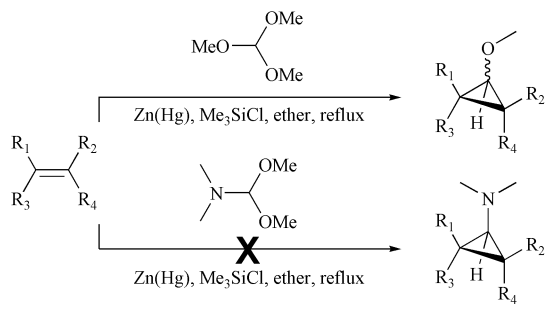
Amidocyclopropanes are readily prepared by reaction of *N*-diethoxymethyl amides with alkenes in the presence of zinc amagalm, zinc chloride and chlorotrimethylsilane.

The aminocyclopropyl unit is present in a significant number of natural and non-natural biologically active compounds.[1] The traditional approach to this unit generally involves cyclopropanation of an olefin using a diazoester followed by Curtius rearrangement.[2] More recently, in an elegant variant of the Kulinkovich reaction, the de Meijere group[3] has shown that the titanium-mediated cyclopropanation of *N*,*N*-dialkyl-carboxamides provides a useful alternative strategy. The direct cyclopropanation of olefins using stoichiometric chromium based (alkoxycarbonyl)dialkylaminocarbene complexes has also been reported by Barluenga *et al.* [4] for the special case of geminally functionalised cyclopropyl amino acids.

We have previously shown that organozinc carbenoids[5] can be generated from carbonyl groups[6] and acetals[7] with zinc and chlorotrimethylsilane and that these intermediates can then undergo cyclopropanation reactions. Of particular interest in the present context was our observation that the selection of an orthoformate as a reagent provided an efficient carbenoid precursor for the formation of alkoxycyclopropanes (Scheme 1).[8]

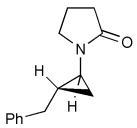
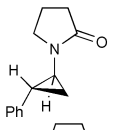
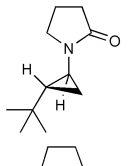
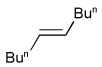
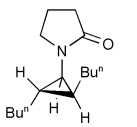
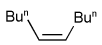
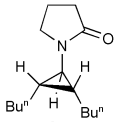
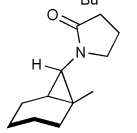
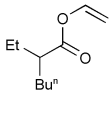
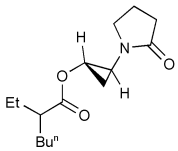
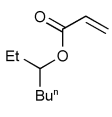
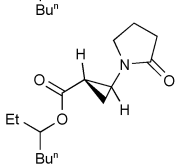
As a logical consequence of the above sequence we therefore elected in the first instance to study the possibility of generating hitherto unknown α-amino organozinc carbenoids using dimethyl formamide dimethylacetal as "an analogous reagent". In the event however, under the experimental conditions used for alkoxycyclopropanation[8] no cyclopropanation reaction occurred (Scheme 1). We therefore reasoned that the incorporation of an additional electron-withdrawing group on the nitrogen atom, such as an acyl group, could be expected to attenuate the electron-donating ability of the amino function and thus affect the generation, stability and the reactivity of the resultant carbenoid. Such modifications have been applied to Fischer aminocarbenes and are known to make the complexes more similar to alkoxycarbenes in character.[9] In order to examine the above hypothesis, the cyclopropanating ability of the carbenoid generated from *N*-diethoxymethyl 2-pyrrolidinone **1** was accordingly investigated. The required substrate is simply prepared by reaction of 2-pyrrolidinone with triethylorthoformate in the presence of a catalytic amount of aluminium chloride.[10]



Scheme 1

A preliminary study using allylbenzene as the alkene component and **1** as the α-amidocarbenoid source was then used to develop a convenient experimental method† and, as revealed in Table 1 (entry 1), the desired amidocyclopropane derivative could be formed smoothly and in high yield. From a practical standpoint, and in contrast both to the classical Simmons–Smith reaction[11] and to our own alkoxycyclopropanation reaction,[8] it was particularly gratifying that high yields could be obtained using only a two fold excess of reagent **1** relative to the alkene.

Table 1 Cyclopropanation of alkenes using **1**

Entry	Alkene	Products	*trans* : *cis*[a]	Yield (%)
1			11.5 : 1	88
2			1.1 : 1	70
3			> 95 : < 5	61
4			—	83
5			1 : 1	52
6			1.3 : 1	63
7			2 : 1	57
8			1 : 1	9

[a] Determined using NMR spectroscopy. For convenience, only the *trans*/*exo* isomer is shown.

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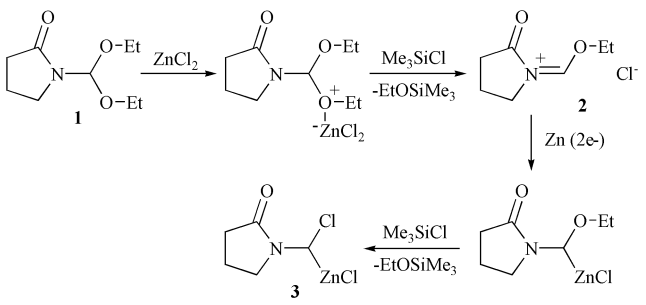
Further examination of the results in Table 1 confirms that preparatively useful yields of amidocyclopropanes can be obtained from mono- (entries 1–3), di- (entries 4 and 5) and tri- (entry 6) substituted alkenes and that reaction occurs with retention of the original alkene geometry (entries 4 and 5). In terms of potential chemoselectivity it is of interest to note that the reaction of the electron rich enol ester (entry 7) is clearly much more efficient than that of the α,β-unsaturated ester (entry 8) under identical conditions. Although the stereochemical outcome of these reactions can clearly be influenced by substrate structure (compare entries 1 and 2), it is also significant that there is a distinct preference for the formation of the less hindered *trans* (or *exo*) isomer (entries 1–3, 6 and 7). This stands in direct contrast to the behaviour of other functionalised organozinc carbenoids which we have studied.[5,8]

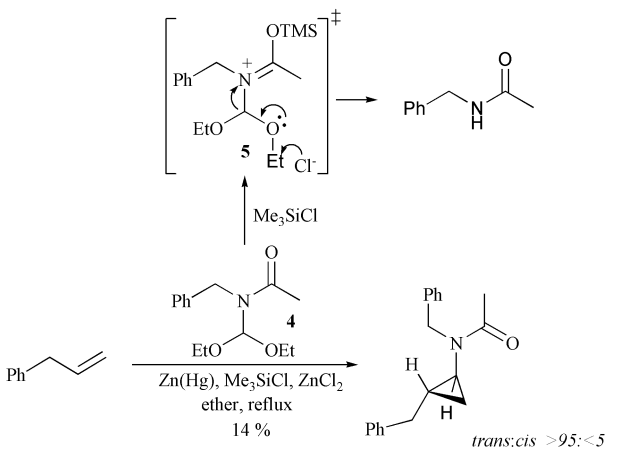
From a mechanistic standpoint, a plausible sequence for the formal generation of the α-amidoorganozinc carbenoid from **1** is shown in Scheme 2 and involves Lewis acid assisted cleavage of one ethoxy group by chlorotrimethylsilane and subsequent two electron reduction of the resultant acyliminium ion **2** (or its covalent congener). Reaction with a second equivalent of chlorotrimethylsilane then furnishes carbenoid **3**.

We have also carried out a brief exploratory study of reagent variation which indicates that the corresponding *N*-diethoxymethyl derivative of an acyclic amide *e.g.* **4** provides the desired product in much lower yield. The fact that the principal product is the starting amide may indicate, as implied in Scheme 3, that competitive silylation on oxygen provides a facile pathway for elimination of ethyl formate *via* **5**. The formation of an analagous intermediate from the cyclic derivative **1** is of course less favourable on grounds of ring strain.

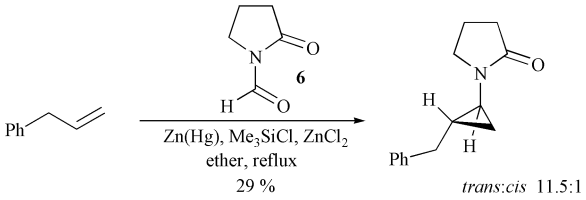
We have also investigated the reactivity of *N*-formyl-2-pyrrolidinone **6** using different silicon electrophiles such as chlorotrimethylsilane, trimethylsilyl triflate and 1,2-bis (chlorodimethylsilyl) ethane. However even although the formyl carbonyl is, as expected, the more reactive, this carbenoid precursor appears to be less efficient with the best result achieved using chlorotrimethylsilane (Scheme 4) (*cf.* entry 1 in Table 1).



Scheme 2



Scheme 3



Scheme 4

This experiment also provides strong presumptive evidence that *N*-formyl pyrrolidinone is not formed *in situ* when **1** is used.

In summary, we have developed a very simple, practical and inexpensive method for the preparation of amidocyclopropanes *via* an entirely novel class of organozinc carbenoid. The study of the scope of this reaction as well as the generation and reactivity of related aminocarbenoid precursors are currently under investigation.

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Notes and references

† General procedure: a solution of *N*-diethoxymethyl 2-pyrrolidinone **1** (2 mmol) in dry diethyl ether (2.5 mL) was added *via* a syringe pump over 2 to 14 h to a vigorously stirred mixture of zinc amalgam (1.30 g), zinc chloride (2 mmol), chlorotrimethylsilane (10 mmol) and alkene (1 mmol) in dry diethyl ether (5.5 mL) under nitrogen at reflux. The mixture was stirred for 6 hours and then allowed to cool to room temperature. The reaction was quenched with an aqueous saturated sodium bicarbonate solution and after stirring for 20 minutes, the mixture was filtered through celite and the separated zinc washed with diethyl ether and dichloromethane. The organic solvents were removed *in vacuo* and the aqueous layer was extracted with diethyl ether. The combined organic extracts were washed with brine, dried ($MgSO_4$), filtered and concentrated *in vacuo*. The crude product was purified by flash column chromatography to give the desired amidocycloproprane as a mixture of isomers.

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