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LETTERS

Observations on the Generation of Organozinc Carbenoids from Acetals and Ketals

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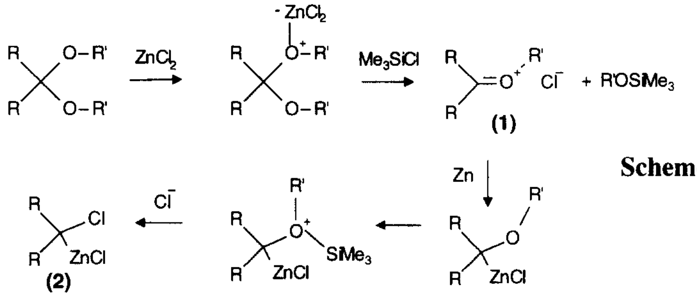
Abstract: The use of acetals and ketals as direct precursors for organozinc carbenoid chemistry is illustrated by their direct conversion to alkenes in a one pot operation. Aryl acetals can also be used as precursors for the cyclopropanation of cyclohexene. © 1998 Elsevier Science Ltd. All rights reserved.

We have previously shown that organozinc carbenoids[1] generated from the reaction of readily available carbonyl compounds with zinc in the presence of a silicon electrophile may be usefully employed in a variety of reactions including direct deoxygenation to give alkenes via C-H insertion,[2] dicarbonyl coupling,[3] and cyclopropanation.[4a,b]

From a mechanistic standpoint, the fact that the reaction proceeds *via* single electron transfer from zinc to the carbonyl group was demonstrated in an elegant series of intramolecular trapping experiments by Corey and Pyne.[5] Moreover, as postulated by Burden[6] for the case of the Clemmensen reduction with which a mechanistic parallel may be drawn, the formation of unwanted pinacolic coupling products in such systems is most readily explained by the formation of a carbon centred radical possessing a zinc oxygen bond as an early intermediate. We were therefore intrigued to note that the groups of Hegedus and Hossain have reported multistep procedures for the preparation of isolable organochromium[7] or organoiron[8] carbenoids in which the key step involves two electron delivery from a metal salt to a preformed carboxonium salt derived from an orthocarbonate or acetal.

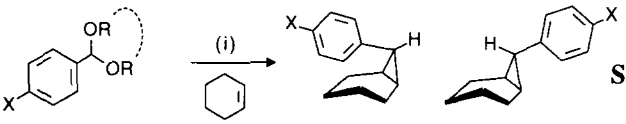


Scheme 1

PII: S0040-4039(98)01001-6

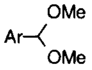
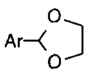
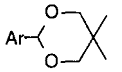
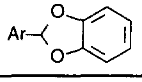
We therefore reasoned, as implied in **Scheme 1,** that the selection of an acetal or a ketal would lead, *via* Lewis acid assisted cleavage[9], to on oxonium intermediate (**1**) which, by virtue of its positive charge, would be more likely to accept two electrons from zinc, and evolve as indicated to the organozinc carbenoid (**2**). Furthermore, such a pathway would circumvent the formation of radical intermediates possessing a zinc oxygen bond.

The above argument presupposes however that the regeneration of the parent carbonyl compound does not occur *via* alkyl oxygen cleavage of oxonium ion (1) by chloride anion.[10] While such a pathway is either unlikely or impossible for certain substrates (*vide infra*), this possibility was examined in a series of NMR experiments using the reaction of 2-pentadecyl-1,3-dioxolane with chlorotrimethylsilane both in the presence and the absence of zinc chloride. These studies indicated that the starting material was not consumed and that the parent aldehyde was not formed to a significant extent. With the above considerations in mind we now report the our preliminary results on the behaviour of a range of acetals and ketals in a series of prototypical reactions as outlined below.

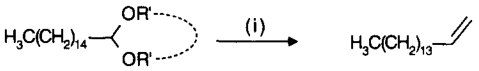


Scheme 2

(i). Reagents and Conditions: 10 eq Zn(Hg), 4 eq Me_3SiCl, 1 eq $ZnCl_2$, Et_2O reflux.

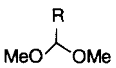
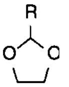
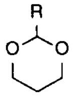
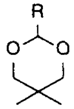
Entry	**Acetal**	**X**	**Yield (%)**	**Ratio** (endo:exo)
1		Me	34	5.6 : 1
2		OMe	65	23.5 : 1
3		Me	38	6.1 : 1
4		H	51	3.3 : 1
5		Cl	30	2.9 : 1
6		H	43	3.5 : 1
7		H	20	4 : 1
8		OMe	20	5 : 1

The trapping of organozinc carbenoids derived from a series of *para*-substituted aryl acetals with cyclohexene was selected for initial study. Examination of the tabulated results in **Scheme 2** confirms the above hypothesis, with the relative efficiencies of carbenoid generation and the observed diastereomeric preference for endo adduct formation tending to mirror those already noted and rationalised for the free aldehyde.[1,4a] In terms of acetal variation, the successful trapping of the catechol derived substrates (entries 7 and 8) is of clear mechanistic significance since carbonyl regeneration would require aryl oxygen cleavage by *ipso* substitution. In similar fashion, the isolation of comparable yields of cyclopropane from the dioxane (entry 4) and the neopentyllic 1,3-dioxane (entry 6) also argue against the intermediacy of the free aldehyde and suggest that the formation of a relatively low energy benzylic oxonium cation is a dominating feature in this instance.



Scheme 3

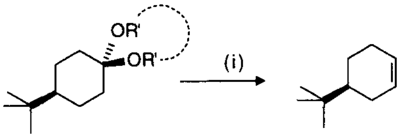
(i) Reagents and Conditions: 10 eq Zn(Hg), 4 eq Me_3SiCl, Et_2O reflux.

Acetal **R=$H_3C(CH_2)_{14}$**				
Entry	1	2	3	4
Time (h)	20	17	36	60
Yield (a)	62	86	6 (84)	14 (80)

(a) Yields in parenthesis are of recovered starting material

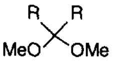
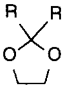
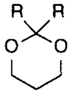
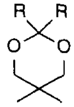
It was therefore of interest to explore the reactivity profile in the case of four of the more common acetal protecting groups derived from the simple linear aliphatic aldehyde, hexadecanal (**Scheme 3**). In this instance, the fate of the carbenoid is to undergo insertion into the neighbouring C-H bond, as demonstrated by the reaction of the free aldehyde itself to give the terminal alkene in 82% yield. Inspection of the results in **Scheme 3** indicates that, in contrast to the aromatic aldehydes, the nature of the acetal can pay a determining role in the reaction. Thus, while the 1,3-dioxolane and dimethyl acetal derivatives (entries 1 and 2 respectively) gave the alkene in preparatively useful yield, the corresponding six membered ring, 1,3-dioxane acetals (entries 3 and 4) were essentially inert under the reaction conditions.

The paramount importance of the overall substrate structure in facilitating oxonium ion formation was further reinforced through a study of the corresponding series of ketals derived from 4-^{t}butyl cyclohexanone (**Scheme 4**) where, once again, in marked contrast to the aliphatic aldehyde derivatives, all four derivatives yielded the alkene in essentially comparable yield.



Scheme 4

(i) Reagents and Conditions: 10 eq Zn(Hg),4 eq Me_3SiCl, Et_2O reflux.

Ketal **R-R = 4-^{t}Butylcyclohexyl**				
Entry	1	2	3	4
Time (h)	16	16	14	17
Yield (a)	56	59	50	52

(a) Isolated as the dibromide

All of the above observations are in keeping with a mechanistic rationalisation in which cleavage to an oxonium ion is a rate limiting step which is strongly influenced by the nature of the substrate, both in terms of the ability of the structure of the parent carbonyl compound, aldehyde or ketone, to stabilise the positive charge, and also, for the acetal or ketal, in terms of relief of ring strain and entropic factors. An obvious parallel can be drawn with the faster rates of hydrolysis of acetals relative to ketals, and with the known relative rates as a function of the cyclic or acyclic nature of the protecting group.[11]

Irrespective of the merits or otherwise of the above mechanistic hypothesis, the direct deoxygenation of an acetal or a ketal is a preparatively useful transformation which has not previously been accomplished in a single step. Furthermore, the ability to preselect an acetal which will, or will not, function as an organozinc carbenoid precursor, when combined with the known tolerance of the chlorotrimethylsilane-zinc system towards remote ester and even halogen functionality,[2] provides opportunities for highly chemoselective transformations in more complex systems.

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References and Notes

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9. Initial oxonium ion formation can be considered to result either from adventitious protonation or from the zinc chloride which would also be formed. The oxonium ion formation thus becomes more facile as the reaction proceeds and more zinc chloride is produced. Alternatively, as in **scheme 2**, additional zinc chloride may be added from the outset of the reaction.
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