

The generation and trapping of organozinc carbenoids from orthoformates: a novel alkoxycyclopropanation reaction

Rodney J. Fletcher, William B. Motherwell* and Matthew E. Popkin

Department of Chemistry, Christopher Ingold Laboratories, University College London, 20 Gordon Street, London, UK
WCIH OAJ

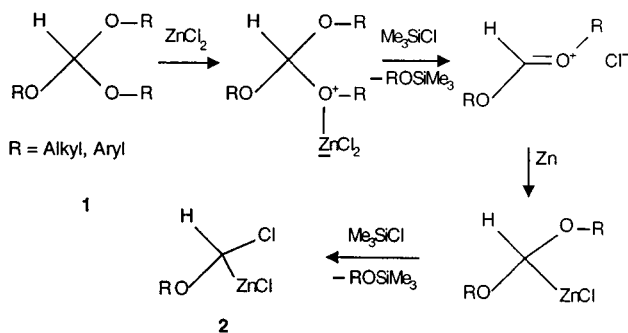
Alkoxycyclopropanes are readily prepared by reaction of an orthoformate with an alkene in the presence of Me_3SiCl and zinc.

We have previously shown that a useful range of organozinc carbenoids¹ can be generated from the reaction of simple carbonyl compounds with zinc in the presence of a silicon electrophile and that these intermediates can then undergo a variety of reactions including C–H insertion to give alkenes,² dicarbonyl coupling³ and cyclopropanation.⁴ More recently, in the light of reports on the preparation of isolable organochromium⁵ and organoiron⁶ carbenoids *via* two-electron delivery from a metal salt to a preformed carboxonium salt, we have demonstrated that acetals and ketals may be used as precursors for the formation of related organozinc carbenoids *via* reduction of their derived oxonium ions, once again with zinc in the presence of Me_3SiCl .⁷

As a logical consequence of the above sequence, and in view of the proven versatility of alkoxycyclopropanes as highly useful intermediates for organic synthesis,⁸ we therefore reasoned, as outlined in Scheme 1, that the Lewis acid assisted cleavage of an orthoformate **1** could give rise, in similar fashion, to hitherto unknown α -alkoxy and α -aryloxy organozinc carbenoids **2**.

A preliminary study using allylbenzene and trimethyl orthoformate as a convenient methoxycarbenoid source served to confirm the above hypothesis (Table 1, entry 1) and also allowed us to develop a convenient experimental method. Thus, a typical experimental procedure would involve slow addition over 24 h of two separate portions of trimethyl orthoformate (1.4 ml, 8 mmol) and Me_3SiCl (1.0 ml, 8 mmol) in Et_2O to a vigorously stirred mixture of the alkene (2 mmol), Me_3SiCl (1.2 ml, 0.9 mmol) and zinc amalgam (2.5 g, 50 mmol) in refluxing Et_2O , each completed addition being followed by a 24 h reflux.

Further inspection of the results in Table 1 using a series of simple alkenes not only emphasises that preparatively useful yields of methoxycyclopropanes can be obtained under mild conditions, but also confirms that cyclopropanation occurs with retention of the original stereochemistry of the alkene (entries 3 and 4), that mono-, di- and tri-substituted alkenes can be used



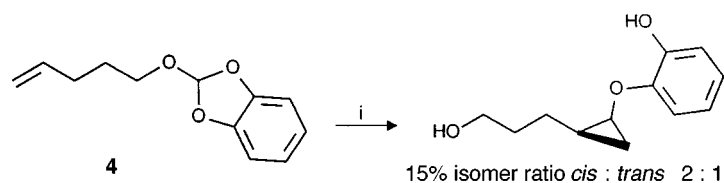
(entries 1–5) and that, as for other organozinc carbenoids,^{1,4} there is a distinct stereochemical preference for formation of the more hindered *cis* (or *endo*) isomer (entries 1, 3 and 5).

Our attention was then directed towards the use of a variety of readily available orthoformates in order to assess their relative efficiencies for alkoxy- and aryloxy-carbenoid generation. Comparison of the results in Table 2 using allylbenzene as the standard alkene trap reveals several features of interest. Thus, the selection of tripropyl orthoformate (entry 1) led to a significant decrease in the isolated yield when compared with its trimethyl congener (Table 1, entry 1), presumably as a result of increased steric hindrance for incipient oxonium ion formation and/or electron delivery. However, the ability to preselect an unsymmetrical orthoformate with improved leaving group ability can be advantageous, as in the case of diethyl phenyl orthoformate (entry 2) which afforded only the ethoxycyclopropane in good yield. Furthermore, the obvious parallel which can be drawn in terms of the relative contributions of relief of ring strain and entropic factors involved in the

Table 1 Methoxycyclopropanation of alkenes using trimethyl orthoformate

Entry	Alkene	Products	Isomer ratio ^a	Yield (%)
1			2 : 1	64
2			2 : 1	56
3			10 : 1	53
4			—	56
5			5 : 2	65

^a Determined using NMR spectroscopy. For convenience, the major *cis* isomer is shown.



Scheme 2 Reagents and conditions: i, Zn/Hg (34 equiv.), Me₃SiCl (5 equiv.) Et₂O, reflux

Table 2 Alkoxy- and aryloxy-cyclopropanation of allylbenzene using orthoformates

Entry	Orthoformate	R	Isomer ratio ^a (%)	Yield (%)
1	(PrO) ₃ CH	Pr	2 : 1	43
2	(EtO) ₂ CH(OPh)	Et	2 : 1	67
3		CH ₂ CH ₂ OSiMe ₃	3 : 1	55
4		2-hydroxyphenyl	5 : 2	23

^a Determined using NMR spectroscopy. For convenience, the major *cis* isomer is shown in 3.

hydrolysis of acetals, ketals and orthoesters⁹ can be used to exercise some degree of predictive power, as evidenced by the selective transfers involved in the use of the 2-methoxydioxolane (entry 3) and the catechol derivative (entry 4).

Clearly a useful range of functionalised alkoxy- and aryloxy-cyclopropanes can now be constructed in this way.

Finally, we have also carried out a preliminary study in order to probe the electronic character of α -alkoxyorganozinc carbenoids. *A priori* it might be argued that such species could be more nucleophilic, and exhibit a chemoselective preference for an electron-deficient alkene. In the event however, as shown by some representative examples in Table 3, the enol ester (entry 1) and the acrylate (entry 2) give comparable yields of cyclopropanated product. However, the result of a direct competition experiment using the monoterpene ester (entry 3) clearly demonstrates that the more electron-rich alkene is favoured over the acrylate.

From a practical standpoint, as in the classical Simmons–Smith reaction,¹⁰ the above method clearly requires the use of an excess of reagents for efficient organozinc carbenoid generation and trapping. This is reflected in the (potentially intramolecular) aryloxy-cyclopropanation of the unsaturated orthoformate 4 (Scheme 2), where of course only 1 equiv. of alkoxy-carbenoid can be produced.

In summary, the above results exemplify a simple and inexpensive method for the preparation of alkoxy- and aryloxy-cyclopropanes under mild neutral conditions *via* a novel class of organozinc carbenoids. Furthermore, in comparison to traditional methods for the generation of alkoxy-carbenoids, the present method obviates the necessity for handling toxic α -halo

Table 3 Alkoxy-cyclopropanation of various alkenes with orthoformates

Entry	Orthoformate	Substrate	Product	Isomer Yield ratio ^a (%)
1	(MeO) ₃ CH			3 : 1 46
2	(MeO) ₃ CH			3 : 1 ^b 43
3	(EtO) ₃ CH			2 : 1 ^c 44

^a Determined using NMR spectroscopy. For convenience, the major isomer is shown. ^b In this case the major isomer was not assigned. ^c 3 : 1 (*E/Z*) mixture of isomers was employed as substrate.

and α,α -dihalo ether precursors,¹¹ or the multistep procedures involved in the preparation of stoichiometric Fischer carbenoids.¹²

We thank the EPSRC for the award of a postdoctoral fellowship (to R. J. F.) and University College, London, for the provision of a postgraduate studentship (to M. E. P.).

Notes and References

- For a review, see C. J. Nutley and W. B. Motherwell, *Contemp. Org. Synth.*, 1994, 219.
- W. B. Motherwell, *J. Chem. Soc., Chem. Commun.*, 1973, 935.
- A. K. Banerjee, M. C. S. Carrasco, C. S. V. Frydrych-Houge and W. B. Motherwell, *J. Chem. Soc., Chem. Commun.*, 1986, 803; C. A. M. Afonso, W. B. Motherwell, D. M. O'Shea and L. R. Roberts, *Tetrahedron Lett.*, 1992, **33**, 3899.
- W. B. Motherwell and L. R. Roberts, *J. Chem. Soc., Chem. Commun.*, 1992, 1582; W. B. Motherwell and L. R. Roberts, *Tetrahedron Lett.*, 1995, **36**, 1121.
- R. Imwinkelried and L. S. Hegedus, *Organometallics*, 1988, **7**, 702.
- R. D. Theys and M. M. Hossain, *Tetrahedron Lett.*, 1992, **33**, 3447; H. Dy, F. Yang and M. M. Hossain, *Synth. Commun.*, 1996, **26**, 1371.
- W. B. Motherwell, D. J. R. O'Mahony and M. E. Popkin, *Tetrahedron Lett.*, 1998, **39**, 5285.
- E. Wenkert, *Acc. Chem. Res.*, 1980, **30**, 27.
- S. W. Smith and M. S. Newman, *J. Am. Chem. Soc.*, 1968, **90**, 1249; R. M. Hahn and C. S. Hudson, *J. Am. Chem. Soc.*, 1944, **66**, 1909; S. A. Barker and E. D. Bourne, *Adv. Carbohydr. Chem.*, 1952, **7**, 137; M. S. Newman and R. S. Harper Jr., *J. Am. Chem. Soc.*, 1958, **80**, 6350.
- H. E. Simmons, T. L. Cairns, S. A. Vladuchick and C. H. Hoiness, *Org. React.*, 1973, **20**, 1.
- U. Schöllkopf and G. J. Lehmann, *Tetrahedron Lett.*, 1962, **4**, 165; U. Schöllkopf, J. Paust, A. Ali-Azrak and H. Schumacher, *Chem. Ber.*, 1966, **99**, 3391.
- M. Brookhart and W. B. Studabaker, *Chem. Rev.*, 1987, **87**, 411.

Received in Cambridge, UK, 6th August 1998; 8/06208K