Intra- and Intermolecular Reactions of Nucleophilic Carbenes

John Warkentin

Department of Chemistry, McMaster University, Hamilton, Ontario, L8S 4M1, U.S.A.

Abstract: General properties of nucleophilic carbenes are addressed briefly. The preparation of oxadiazoline precursors of such carbenes, and some of their chemical reactions, are presented. Intramolecular reactions include rearrangement and attack by the carbene center on a tethered functional group. Intermolecular reactions include nucleophilic attack at the carbonyl carbon of isocyanates and at the triple bond of dimethyl acetylenedicarboxylate.

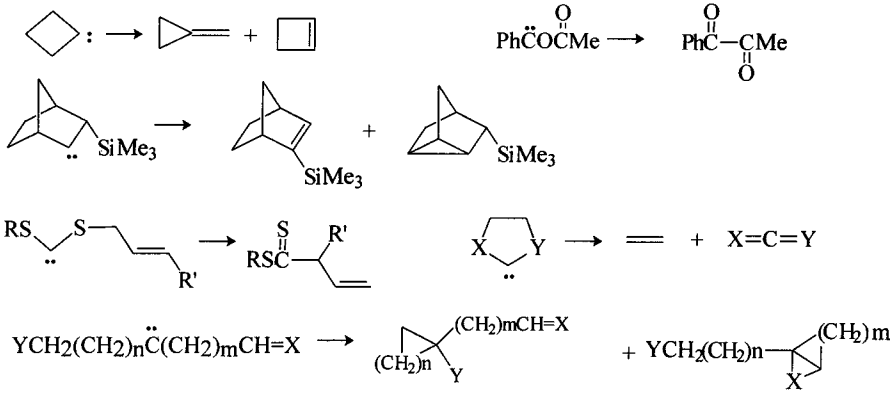
INTRODUCTION

Nucleophilic carbenes are more reactive toward electron-deficient sites than toward electron-rich sites. For example, the nucleophilic dimethoxycarbene does not react with butenes (Ref. 1) but attacks the carbonyl carbon of fluorenone (Ref. 2). Systematic classification of carbenes into electrophilic, ambiphilic, and nucleophilic categories has been reported by Moss, et al. (Ref 3). A carbene's nucleophilicity stems from the ability of substituents to donate electron density to the carbene carbon in the singlet ground state (Ref. 1) of the carbene and in the transition state for attack at an electrophilic site.

Some intramolecular reactions of nucleophilic carbenes are analogous to those of electrophilic carbenes, except for substituent effects on the rate constant. For example, the slow 1,2 H-migration (*ca* 10^4 s^{-1}) (Ref. 4) in neopentylmethoxycarbene compared to that in dimethylcarbene (*ca* 10^7 s^{-1}) (Ref. 4) can be attributed in part to lowering of the ground state energy of the former by conjugation. Conjugation with methoxy groups also shows up in a large singlet/triplet energy gap, computed to be *ca* 76 kcal mol^{-1} in dimethoxycarbene (Ref. 1) compared to *ca* 2 kcal mol^{-1} in dimethylcarbene (Ref. 5). Although 1,2-H migrations are most common, intramolecular reactions of carbenes also include 1,2-alkyl migrations, as in cyclobutylidene (Ref. 6), acyl migrations, as in phenylacetoxycarbene (Ref. 7), silyl migrations (Ref. 8), [2,3]-sigmatropic rearrangements (Refs. 9-11), fragmentations to ethylene

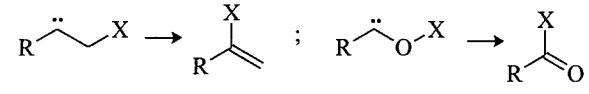
 CCC 1022-1360/98/$ 17.50

and heterocumulene (Refs. 12, 13), and the generalized unimolecular attack of the carbene center at a σ- or π-bond, Scheme 1. Other examples can be found in a large review (Ref. 14).



Scheme 1

Migrations in carbenes must generally be exothermic by roughly the energy of a π-bond (Scheme 2). The greater strength of CO double bonds (*ca* 179 kcal mol-1) compared to CC double bonds (*ca* 146 kcal mol-1) suggests that migrations from oxygen to carbon could have some extra driving force from product stability. That feature is tempered, however, by the ground state stabilization that an oxy substituent provides. To date there isn't any clear evidence that alkyl group migration from oxygen to a carbene carbon is more facile than alkyl group migration from carbon to the same carbene center.



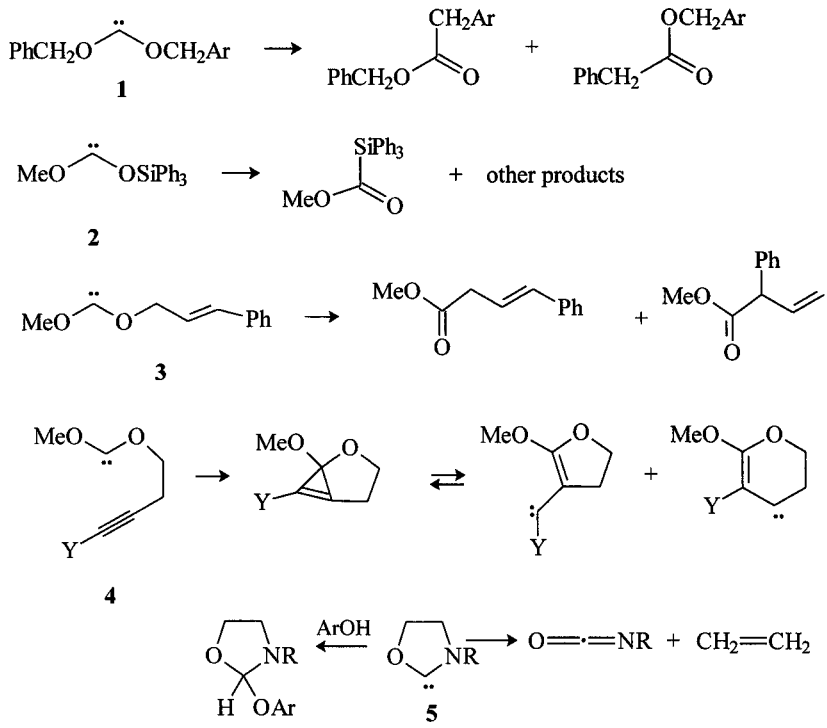
3 sigma bonds 3 sigma + pi

Scheme 2

RESULTS AND DISCUSSION

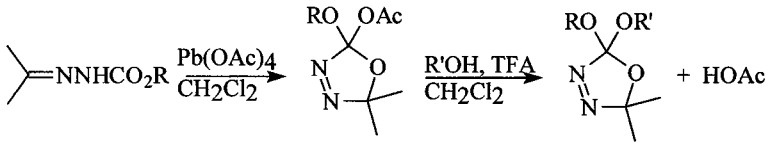
We have explored the chemistry of some potential precursors of dioxycarbenes and aminooxycarbenes including di(benzyloxy)carbenes (**1**), methoxytriphenylsiloxycarbene (**2**), allyloxymethoxycarbenes (**3**), 3-butyne-1-oxycarbenes (**4**), and alkoxyaminocarbenes of the general type **5**, Scheme 3. The first undergo 1,2-benzyl group migration from oxygen to carbon while in **2** the silyl moiety migrates from oxygen to carbon. Carbenes **3** undergo *apparent* overall [1,2]-migrations and [2,3]-sigmatropic rearrangements in competition while **4** undergo attack on the CC triple bond. Carbenes **5** can fragment to ethylene and isocyanate,

but the process is slow enough to permit their intermolecular trapping. Of those carbenes, only **2**, **4**, and **5** are discussed in more detail, because of the time/space limitation and because recent results point to complications from radical chemistry with the precursors of **1** and **3**.



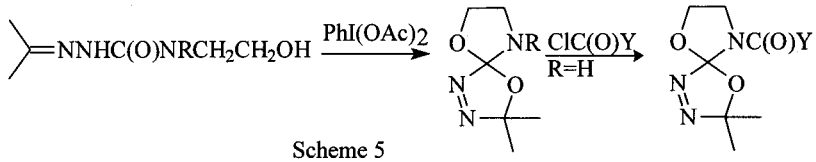
Scheme 3

The precursor was, in each case, an oxadiazoline, prepared by the general procedure (Ref. 15) of Scheme 4 for dioxycarbenes, and according to Scheme 5 for alkoxyaminocarbenes (Ref. 16).



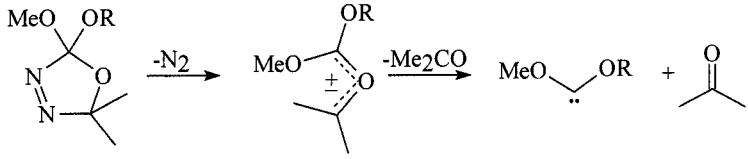
R= Me, $PhCH_2$; R'= $SiPh_3$, $ArCH_2$, $CH_2CH_2C{\equiv}CY$, o-$C_6H_4C{\equiv}CY$

Scheme 4

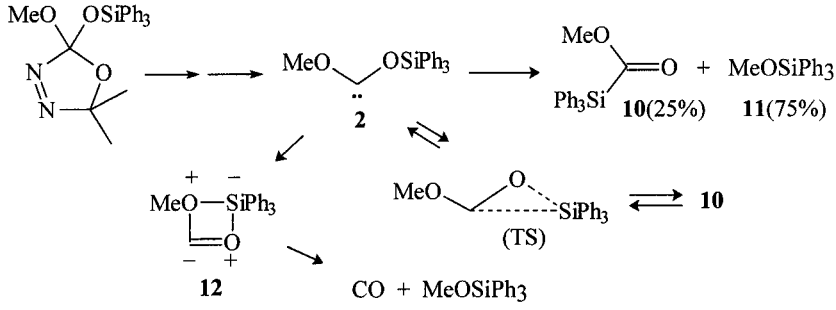


Scheme 5

Oxadiazolines generally undergo thermal cycloreversion to N_2 and a carbonyl ylide in a first step (Refs. 17-20), and that mechanism is assumed to apply in the absence of evidence to the contrary. In a subsequent step the ylide fragments to carbene and carbonyl compound, Scheme 6. Carbene **2**, from thermolysis of the corresponding oxadiazoline, rearranged by migration of the triphenylsilyl group from oxygen to carbon to afford ester **10**, Scheme 7. The major product, however, was ether **11**. Isolation and subjection of **10** to the reaction conditions afforded **11** (Brook rearrangement) (Ref. 21), but too slowly to account for the



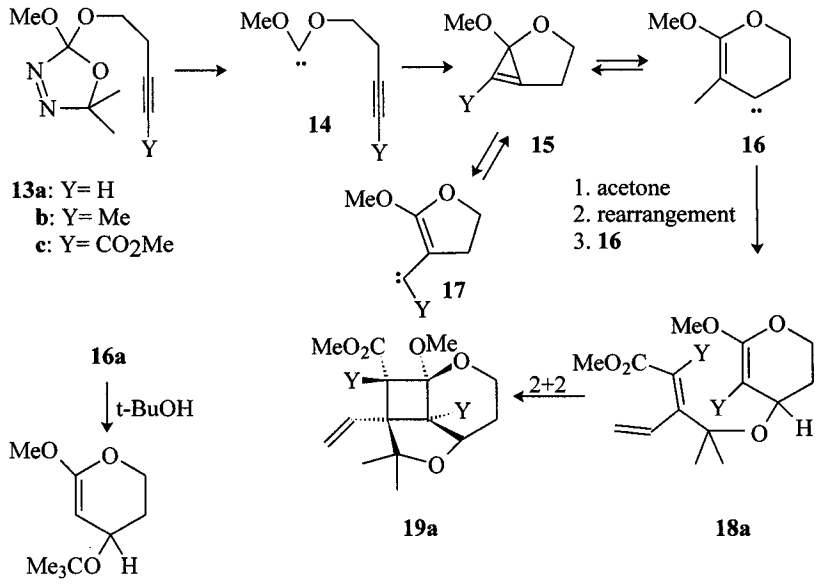
Scheme 6



Scheme 7

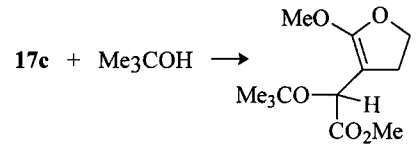
formation of **11** sequentially, *via* **10**, from the oxadiazoline. Thus **10** and **11** are formed from carbene **2** by parallel pathways as in Scheme 7, in which equilibration of carbene **2** with **10**, by 1,2-migration of the Ph_3Si group, is postulated, together with attack of the methoxy oxygen at silicon to generate intermediate (or transition state) **12**. Thermolysis of oxadiazoline **13a** leads sequentially to carbenes **14a** and **16a**, as indicated by results of trapping experiments with t-butyl alcohol (Scheme 8). At a high alcohol concentration, carbene **14a** was intercepted. At a lower alcohol concentration, the first-formed carbene reacted

intramolecularly with the triple bond, leading to carbene **16a**, which was then trapped (Ref. 22). In the absence of added alcohol, **16a** took part in a cascade of reactions through **18a** leading to **19a**, while **16b** stopped at **18b**. From work by the groups of Boger and Nakamura (Refs. 23, 24), with dialkoxy cyclopropenes, it is likely that **15** are intermediates, as shown in Scheme 8.



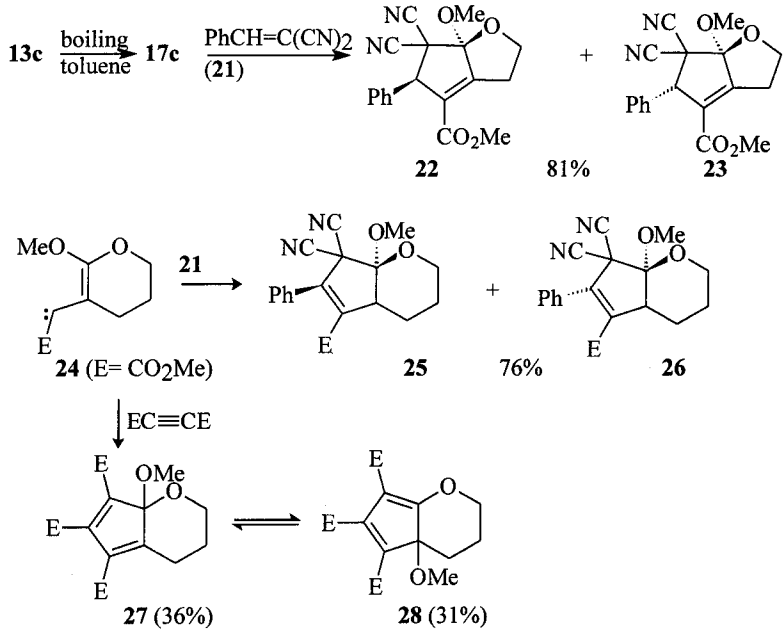
Scheme 8

Cyclopropene **15** might open to either exocyclic carbene **17** or to endocyclic carbene **16** (Scheme 8), and we have explored the effect of substituent Y on the sense of ring opening with Y= Me and Y= CO_2Me, as well as the effect of changing the 2-carbon tether from CH_2CH_2 to benzo. As Scheme 8 shows, the methyl group and H do not cause any difference in the behaviour of carbenes **14**, which apparently afford **16** and, by a subsequent series of reactions, **18** (Ref. 25). The methyl groups are sufficiently hindering, however, to prevent the [2+2] reaction that occurs with **18a**, affording **19a** (Ref. 22). The methoxycarbonyl substituent, on the other hand, causes ring opening to the exocyclic carbene (**17c**, Y=CO_2Me), as determined by trapping with t-butyl alcohol, Scheme 9. Thermolysis of oxadiazoline **13c** (toluene, 110 °C) in the presence of benzylidenemalononitrile (**21**) led to the formation of



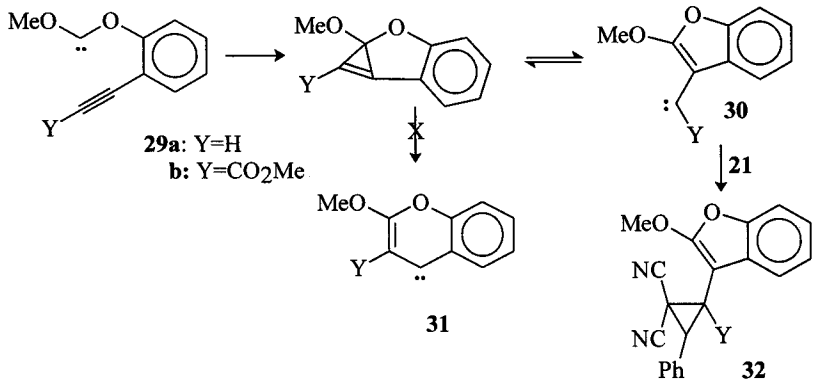
Scheme 9

racemic adducts **22** and **23** (Scheme 10) (Ref. 25). Those are not *normal* 1,3-dipolar cycloaddition products, because carbene **13c** is not a 4 π-electron system, the occupied carbenic orbital being orthogonal to the π-bond (Ref. 26). Boger and coworkers have postulated that analogous reactions (Ref. 23) occur *via* electron transfer from the carbene to **21**; subsequent collapse of the radical-ion pair produces the cyclopentene ring. Carbene **24**, with a 4-atom tether between the carbene site and the triple bond, afforded analogous products with **21**, Scheme 10 (Ref. 25). That carbene also reacted intermolecularly with DMAD, to afford **27** which, by cyclopentadiene isomerization, gave **28**. To our surprise, the benzo analogues of **13a**, **b** (**29a**, **b**) gave rise to species that behaved like carbenes and cyclopropanated **21**, under the same conditions that afforded **22** and **23** from **13a**, **c**, Scheme



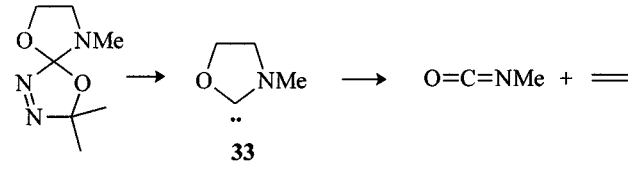
Scheme 10

11 (Ref. 27). The products, **32a** and **32b**, indicate that the benzo tether has two critical effects. First, the initial carbenes (**29**) afford the exocyclic new carbenes (**30**) and not the endocyclic **31**, regardless of whether the substituent is H or CO_2Me. Second, the derived carbenes (**30**) do not enter into electron transfer with **21**, but attack it as a nucleophilic carbene would. The subtle dependence on the tether type (benzo vs CH_2CH_2) can be rationalized in terms of the Boger electron transfer mechanism for formation of cyclopentenes like **22** and **23**. The benzo group presumably stabilizes **30** relative to **31**; **30** being 10 π-electron systems. The benzo group is also electron withdrawing, relative to an alkyl group, making **30** more difficult to oxidize to the corresponding radical cations, relative to corresponding carbenes **17**. Thus **30**, formed preferentially from a cyclopropene precursor (Scheme 11), behave like carbenes toward **21**.



Scheme 11

Alkoxyaminocarbene **33**, generated from the oxadiazoline, can fragment to methyl isocyanate and ethylene, as indicated by formation of hydantoin **34** as a minor product (Refs. 16, 28-30). That hydantoin could be prepared in good yield by inclusion of methyl isocyanate in the thermolysis tube and the analogous compound was obtained when phenyl isocyanate was the carbene trap, Scheme 12. These results indicate that **33** does not fragment rapidly enough to make trapping difficult, in agreement with Sauers' computed barrier of 17.6 kcal mol^{-1} (Ref. 31). Carbenes of type **35** also attack DMAD, affording **36** as a major product. These reactions can be rationalized in terms of nucleophilic attack by the carbene at sp^2 or sp^3 carbon, Schemes 12, 13 (Refs. 16, 28, 29). Presumably corresponding three-membered rings (not shown in Schemes 12, 13) are equilibrated with the dipoles drawn, making those reactions analogous to the intramolecular reactions of Scheme 8. Insertions into phenolic OH bonds



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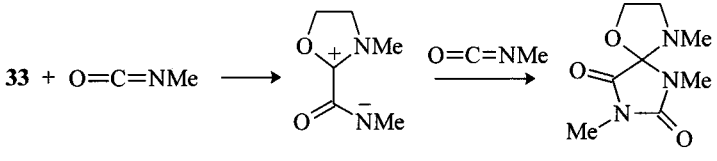

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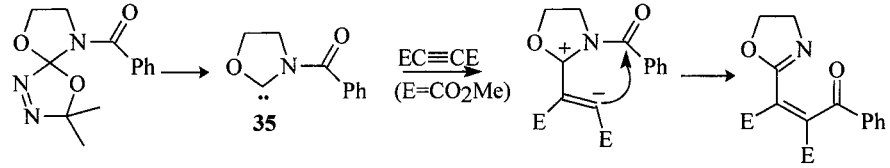
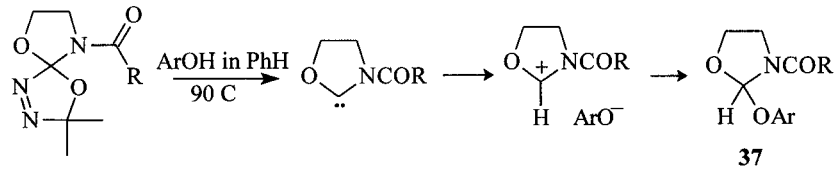
Scheme 12



Scheme 13 **36** (73%)

went in high yields, affording orthoformate analogues **37**, Scheme 14. The process probably involves proton transfer in the first step, as shown, by analogy to insertions of other nucleophilic carbenes into OH bonds (Refs. 32-34).



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R= H, Me, CH_2=C(Me), Ph, OMe; Ar= Ph, 4-NCC_6H_4

Scheme 14

ACKNOWLEDGEMENT

I thank a group of enthusiastic and gifted co-workers, whose names appear in the references, for their contributions, and The *Natural Sciences and Engineering Research Council of Canada* for financial support.

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