

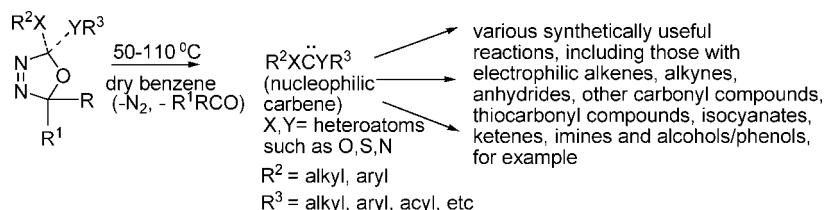
## 2,5-Dihydro-1,3,4-oxadiazoles and Bis(heteroatom-substituted)carbenes

JOHN WARKENTIN

Department of Chemistry, McMaster University, Hamilton, Ontario, Canada

RECEIVED ON MARCH 19, 2008

### CONSPICUOUS



2,5-Dihydro-1,3,4-oxadiazoles with heteroatom substituents at C-2 (also known as corresponding  $\Delta^3$ -1,3,4-oxadiazolines) are very useful materials for the thermal generation of acetoxy(alkoxy)-, dialkoxy-, alkoxy(aryloxy)-, diaryloxy-, alkoxy(alkylthio)-, bis(alkylthio)- and alkoxy(amino)-carbenes. Such carbenes are relatively nucleophilic and react with a variety of electrophilic functional groups. This Account reviews our work to prepare 2,5-dihydro-1,3,4-oxadiazoles and apply them to the synthesis of other target molecules.

Carbenes bearing alkoxy substituents at the carbene carbon can be looked upon as acetals of carbon monoxide. Their reactions with electron-deficient alkenes or alkynes can afford acetals of cyclopropanones or cyclopropenones. Although such products may be formed by concerted cycloaddition, initial formation of one bond to produce zwitterions is likely in some cases. In addition, the reactions of these molecules with carbonyl compounds could involve acetals of  $\alpha$ -lactones as intermediates. Although we have isolated some acetals of cyclopropanones, we have not isolated the other intermediates. However, some of the products we observe probably resulted from these intermediates. For example, dimethoxycarbene reacts with maleic anhydrides to generate six-membered rings by apparent carbonyl addition followed by an acyloxy group transfer. Similarly, dimethoxycarbene reacts with thiocarbonyl compounds, such as xanthates, by apparent carbonyl addition and transfer of the alkylthiyl group to the erstwhile carbene carbon. Reaction of  $ROC:(OR)'$  with an alcohol  $R''OH$  or a phenol should generate chiral (racemic) orthoformates. Similarly, reaction of alkoxy(alkylthiyl) carbenes with alcohols could generate chiral (racemic) dialkyl thyl orthoformates.

2,5-Dihydro-1,3,4-oxadiazoles are particularly useful for synthetic applications because they are easily prepared and reasonably stable, thermal sources of bis(heteroatom)carbenes. Such carbenes react with a variety of electrophilic functional groups, often with rearrangement of initial products. Those products, many of them new, could be used as starting materials toward other synthetic targets. Isolation of products from the reaction is relatively simple because the coproducts of thermolysis of the oxadiazoles are primarily  $N_2$  and a ketone, such as acetone. Thus, 2,5-dihydro-1,3,4-oxadiazoles should be part of every synthesis chemist's toolbox.

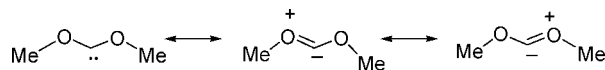
### Introduction

One of the first preparations of dimethoxycarbene (DMC) by thermolysis of 7,7-dimethoxybicyclo-2,2,1-heptadiene derivatives,<sup>1</sup> was published by Hoffmann and Häuser who showed, soon after, that the carbene is nucleophilic.<sup>2</sup> Dimethoxycarbene has a singlet ground state, and it is nucleophilic as suggested by its contributing structures,

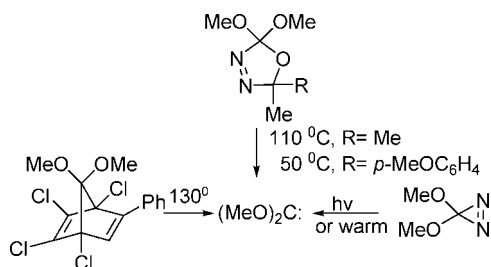
which illustrate interaction of oxygens' unshared electron pairs with a vacancy (p-like orbital) at the carbene site, Scheme 1.

An alternative method for generating that carbene and others photochemically or thermally from diazirines is very useful for the determination of lifetimes and spectra, for example, but less useful for synthetic applications because most

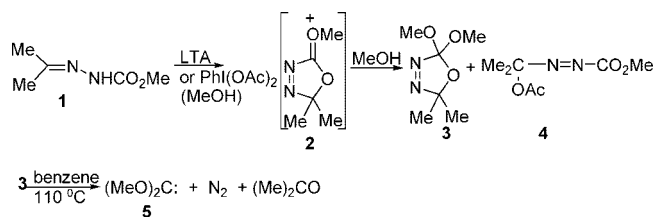
## SCHEME 1



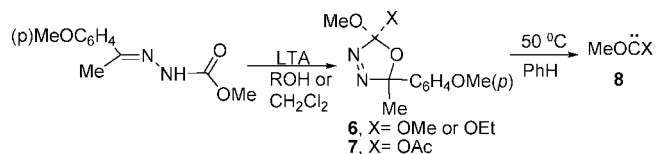
## SCHEME 2



## SCHEME 3



## SCHEME 4

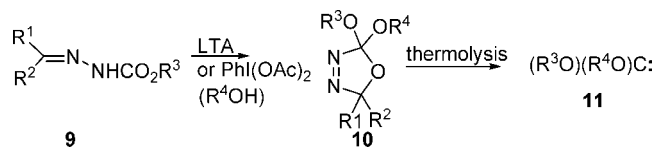


diazirines are explosive,<sup>3</sup> available only in dilute solutions of hexane. 2,5-Dihydro-2,2-dialkoxy-5,5-disubstituted 1,3,4-oxadiazoles are the reagents of choice for many synthetic applications of dialkoxycarbenes, Scheme 2.

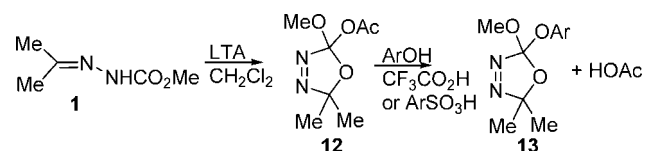
## Synthesis

Synthesis of oxadiazole precursors of various dialkoxy carbenes is relatively simple. Oxidation of the methyl ester of the acetone derivative of hydrazine carboxylic acid (**1**) with lead tetraacetate (LTA)<sup>4</sup> or iodobenzene diacetate<sup>5</sup> in methanol leads to cyclization and formation of 2,5-dihydro-2,2-dimethoxy-5,5-dimethyl-1,3,4-oxadiazole, **3**, probably through intermediate **2**, Scheme 3. An acyclic, minor byproduct **4**, that is formed sometimes, is removed by saponification, and the oxadiazole may be purified further by chromatography or distillation. Thermolysis at about 110 °C, usually in dry benzene in a sealed tube, generates primarily dimethoxycarbene **5**, nitrogen, and acetone, Scheme 3.<sup>4,5</sup> More recently, precursors (**6**, **7**) that thermolyze at about 50 °C were synthesized, Scheme 4,<sup>6a</sup> as well as a bicyclic oxadiazole.<sup>6b</sup> Compounds **6** and **7** must be generated and stored at low temperature to prevent gradual thermolysis and formation of carbene dimer

## SCHEME 5



## SCHEME 6

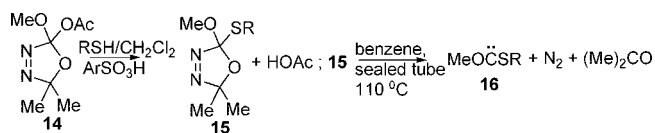


or rearrangement products. With different substituents at C-2, compounds **6** and **7** exist as diastereomers, which does not matter much if the substituents are small (disrotatory motion of C-2 and C-5 substituents) because both produce the same carbene (**8**) upon thermolysis, Scheme 4.

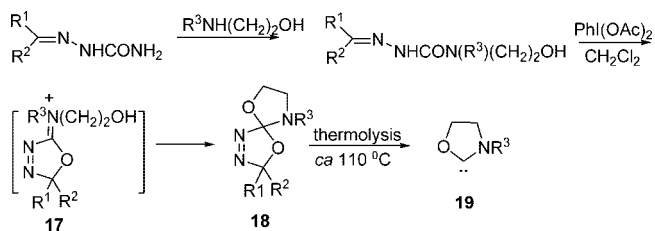
What can be seen at once is that use of a different ester (**9**) in a different alcohol solvent ( $R^4OH$ ) (or  $CH_2Cl_2$  to give the 2-acetoxy-2-methoxy analogue of **3**) or a different ketone in Scheme 3 could produce an analogue of **3**, Scheme 5, and a variety of di(oxygen-substituted)carbenes **11**.<sup>7-9</sup> That is what actually occurs, and very many oxadiazoles of that type have been prepared, some of them diastereomeric.<sup>6</sup> LTA was used most often as the oxidant, attacking hydrazones more rapidly than many other functional groups. Compounds such as phenols are too sensitive to oxidants to survive, but aryloxy groups can be placed at C-2 of the oxadiazole in one of two ways. First, one can use an aryl ester of the hydrazone in a nonoxidizable alcohol.<sup>10</sup> Second, a substitution reaction, in which a 2-acetoxy group in **12** is displaced by an aryloxy group to form **13** under the influence of catalytic acid, Scheme 6, can be used after the oxidation step.<sup>8</sup> Some features of oxadiazole chemistry have been reviewed.<sup>11</sup>

Alcohols and phenols are not the only substituents at C-2 that lead to bis(heteroatom-substituted)carbenes. Alkylthiyl groups and the phenylthiyl group, along with methoxy, have also been introduced at C-2 (**15**) by the substitution method to generate the corresponding carbenes (**16**), Scheme 7.<sup>12</sup> Bis(alkylthiyl)carbenes have also been generated from appropriate oxadiazoles.<sup>13</sup> Spiro-fused amino(oxy)oxadiazoles (**18**) have been prepared as well, as indicated in Scheme 8, by intramolecular ring closure of a probable intermediate **17**.<sup>14</sup>

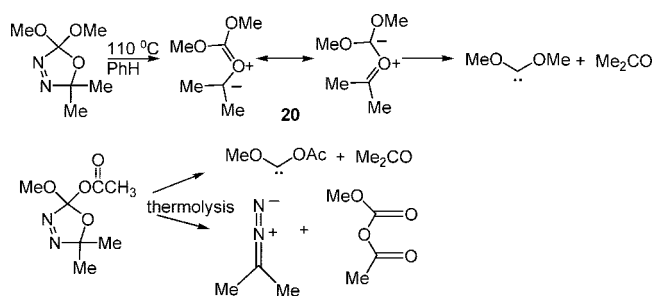
## SCHEME 7



## SCHEME 8



## SCHEME 9



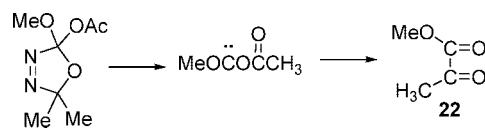
Thermolysis of **18** affords cyclic amino(oxy)carbenes **19**, Scheme 8.<sup>14a</sup>

## Mechanism of Thermolysis

The mechanism of thermolysis of 2,2-dimethoxy-5,5-dimethyl-1,3,4-oxadiazole and of several other 1,3,4-oxadiazoles was established on the basis of computation<sup>15</sup> and experiment.<sup>16</sup> The first step is a 1,3-dipolar cycloreversion, with disrotatory motion of the C-2 and C-5 groups, producing N<sub>2</sub> and a carbonyl ylide intermediate **20**, Scheme 9. The ylide intermediate is short-lived, fragmenting to a ketone and dialkoxy carbene over a barrier of only about 0.4 kcal mol<sup>-1</sup> at 110 °C.<sup>15c</sup> The low barrier suggests that other carbonyl ylides of type **20** are not likely to pass over much higher barriers. For example, the carbonyl ylide from the 2-acetoxy-2-methoxy analogue (**12**) fragments to acetoxy(methoxy)carbene over a barrier of about 2 kcal mol<sup>-1</sup> at 110 °C.<sup>15c</sup> In a few cases, an alternative cycloreversion to afford a diazoalkane and a carbonate has also been observed, Scheme 9.<sup>15a,c</sup> Photolysis of the oxadiazoles does not lead to carbonyl ylides but, instead, primarily to a carbonate and a diazo compound.<sup>17</sup>

The small barrier to fragmentation of such ylides means that their trapping by intermolecular cycloaddition is not likely to succeed, although other carbonyl ylides, such as those with one phenyl substituent, have been intercepted by

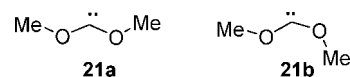
## SCHEME 10



cycloaddition.<sup>18,19</sup> A dialkoxy carbene, on the other hand, can be trapped in both intramolecular and intermolecular processes. For example, reaction with phenol or *t*-butyl alcohol has often been used to indicate that a carbene intermediate was present, and methoxy(propargyloxy)carbene, for example, reacted intramolecularly. Details are provided below.

## Structural, Kinetic, and Thermodynamic Aspects

The UV and visible spectra of DMC at 77 K were reported in 1988,<sup>20</sup> the photoelectron spectrum in 1998,<sup>21</sup> and the infrared spectrum of DMC (matrix isolated) in 2006.<sup>22</sup> Contributions of dipolar structures are manifested through the double-bond character of the carbene-to-oxygen bonds,<sup>22</sup> Scheme 1. DMC is more stable in the *w*-conformation (**21a**) than in the sickle form (**21b**).<sup>21</sup> The heat of formation of DMC was estimated as -61 kcal mol<sup>-1</sup>.<sup>23</sup> The most stable conformations of acetoxy(methoxy)carbene have also been assigned.<sup>24</sup> Rate constants for insertions of dimethoxycarbene into the H-bond of ethanol are about 3.2 × 10<sup>4</sup> s<sup>-1</sup> at 20–25 °C in 1 M EtOH/CH<sub>3</sub>CN,<sup>23</sup> the acidity of the conjugate acid in water was calculated to be 15.5<sup>25</sup> or 11,<sup>26</sup> and the intrinsic barrier to protonation has been estimated as 1–5 kcal mol<sup>-1</sup>.<sup>26</sup>

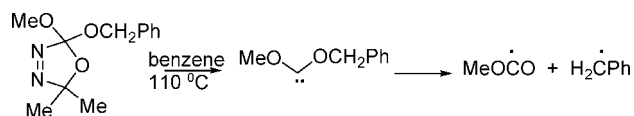


## Reactions of Bis(oxygen-substituted)carbenes

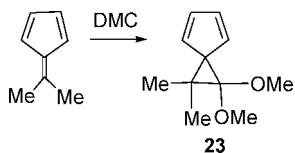
**1. Self-Reactions.** Dimethoxycarbene does not rearrange readily in solution but in the gas phase, at high temperatures, analogous dialkoxycarbenes rearrange to esters.<sup>27</sup> In benzene solution, dimethoxycarbene and asymmetric analogues dimerize to tetraalkoxy ethenes.<sup>1,4</sup> Acetoxy(methoxy)carbene rearranges, by acetyl migration to the carbene center, to methyl pyruvate **22**, Scheme 10,<sup>24</sup> but the rearrangement is not so fast as to preclude some trapping.<sup>6a</sup> Fragmentations to diradicals or radical pairs have also been observed, as in the case of benzyloxy(methoxy)carbene (BMC), Scheme 11.<sup>28–30</sup> Benzyl radicals from BMC were trapped with 2,2,6,6-tetramethylpiperidin-1-oxyl radicals (TEMPO).

**2. Reactions with Alkenes, Alkynes and Dienes.** A second review of some aspects of intra- and intermolecular chem-

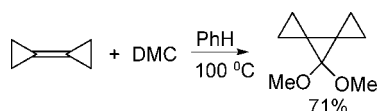
## SCHEME 11



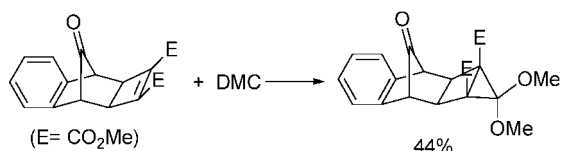
## SCHEME 12



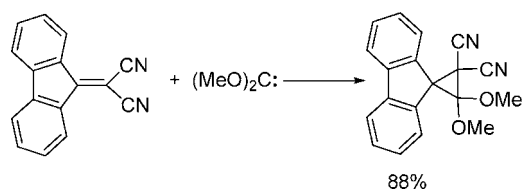
## SCHEME 13



## SCHEME 14



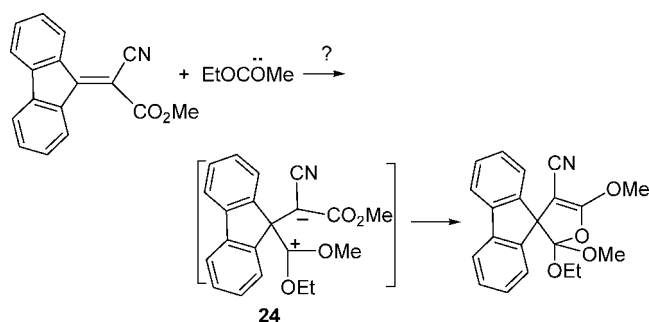
## SCHEME 15



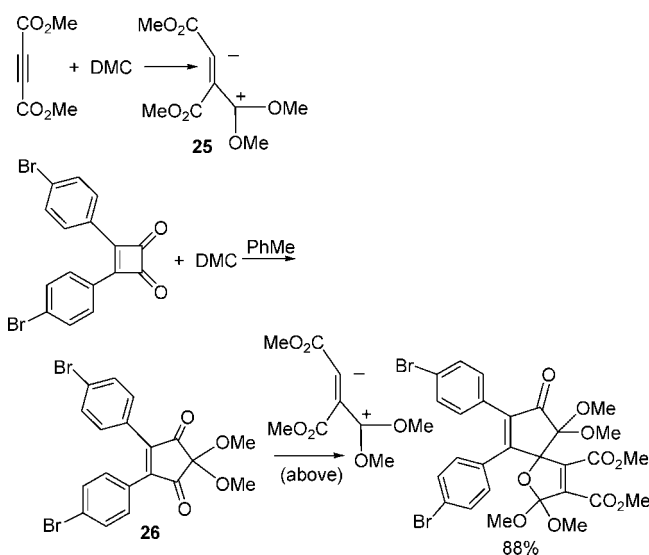
istry of di(oxygen-substituted)carbenes was published in 1998.<sup>31</sup> As expected, the nucleophilic dialkoxy carbenes add to CC multiple bonds that are electron-deficient or strained. 6,6-Dimethylfulvene was used to illustrate the nucleophilicity of DMC, which added to the fulvene to afford 1,1-dimethoxy-2,2-dimethylspiro[2.4]hepta-4,6-diene **23**, an acetal of a cyclopropanone, Scheme 12.<sup>32</sup> Additions to strained or electron-deficient C=C bonds that also afford the dimethyl acetal of a cyclopropanone are illustrated in Schemes 13,<sup>7</sup> 14<sup>33</sup> and 15.<sup>34</sup>

Nucleophilic character gives heteroatom-substituted carbenes, such as dimethoxycarbene, some interesting properties. They react much more slowly ( $k \approx 10^3 \text{ M}^{-1} \text{ s}^{-1}$  for addition of dimethoxycarbene to acrylonitrile)<sup>20</sup> than electrophilic counterparts and fail altogether to add to simple alkenes such as cyclohexene.<sup>35</sup> Dimethoxycarbene added stereospecifically to  $\beta$ -deuteriostyrenes, suggesting that addition to styrene is concerted.<sup>36</sup> However, highly electrophilic alkenes may add nucleophilic carbenes by a stepwise mech-

## SCHEME 16



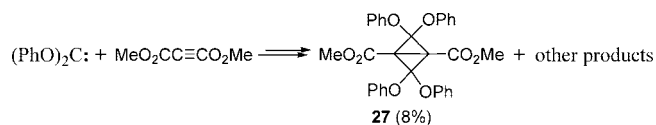
## SCHEME 17



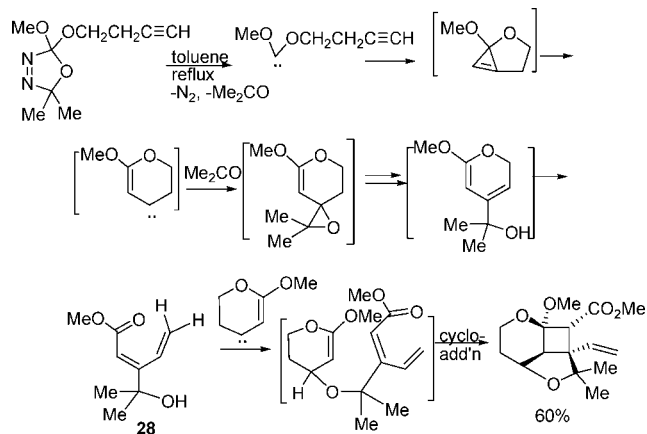
anism or the first formed cyclopropanes may undergo ring-opening and reclosure to isomeric cyclopropanes via zwitterionic transition states.<sup>37</sup> Zwitterionic intermediates **24**<sup>38</sup> can lead to more stable five-membered isomers of cyclopropanes,<sup>38</sup> Scheme 16, although such compounds could also arise by means of concerted 1,4-cycloaddition.

Intermolecular addition to an electron-poor alkyne suggests that stepwise addition to form a zwitterion can occur, as suggested in Scheme 16. Nair and co-workers have developed three-component reactions in which DMC adds to dimethyl acetylenedicarboxylate (DMAD) to afford a zwitterionic intermediate (**25**) that subsequently adds to a site of unsaturation to afford a five-membered ring.<sup>39</sup> In a recent example, addition of DMC to a conjugated cyclobutane-1,2-dione led to a cyclopentene-1,3-dione (**26**), which then reacted by carbonyl addition with a zwitterion from DMC and dimethyl acetylenedicarboxylate (DMAD) to afford a novel product from a three-component reaction, Scheme 17.<sup>40</sup> Although the zwitterion postulate fits, it is conceivable that a cyclopropene is equilibrated with the zwitterion. Product **27**, isolated from reaction

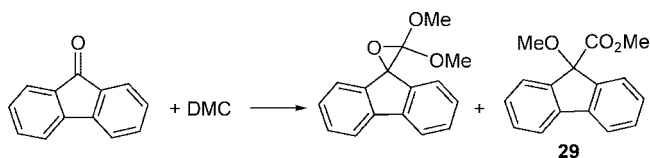
## SCHEME 18



## SCHEME 19



## SCHEME 20



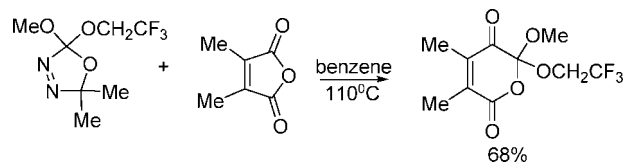
of diphenoxycarbene with DMAD, suggests that a cyclopropene is an intermediate in some cases, Scheme 18.<sup>41</sup>

Another addition of a dialkoxycarbene to an alkyne indicates that an electron-withdrawing group is not required for intramolecular addition. In Scheme 19, which represents a complex sequence of reactions in one pot, some intermediates were inferred from results of deuterium-labeling and incorporation of key intermediates. Intermediate **28** could be isolated.<sup>42</sup>

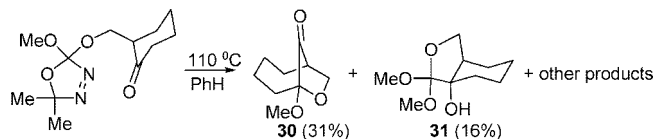
DMC adds to electron-deficient dienes in the 1,4-sense.<sup>43</sup> Addition also occurs to C60.<sup>44</sup>

**3. Reactions with Carbonyl Compounds.** One of the first reactions of a carbonyl compound with DMC that indicated the latter's nucleophilicity was its reaction with tropone. The product, isolated in 41% yield, was that of 1,4-addition.<sup>45</sup> Intermolecular reactions of DMC have since been observed with a variety of carbonyl compounds, Schemes 20<sup>46</sup> and 21,<sup>5</sup> for example. Reaction with 9-fluorenone, Scheme 20, was studied with <sup>18</sup>O and deuterium labeling, which showed that the ester (**29**) is formed from the oxirane by ring-opening of the latter and intramolecular methoxy transfer.<sup>46</sup> A similar intramolecular (carboxylate) transfer was inferred from reaction of DMC with anhydrides, Scheme 21.<sup>5</sup> Intramolecu-

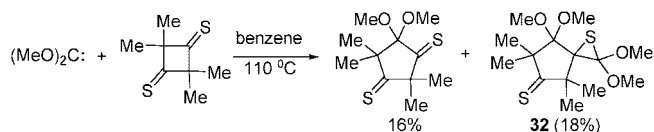
## SCHEME 21



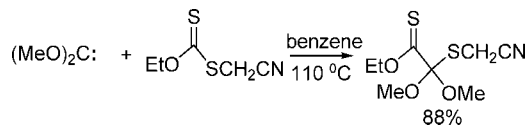
## SCHEME 22



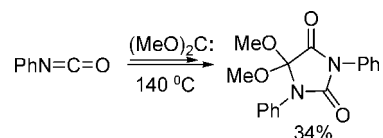
## SCHEME 23



## SCHEME 24



## SCHEME 25

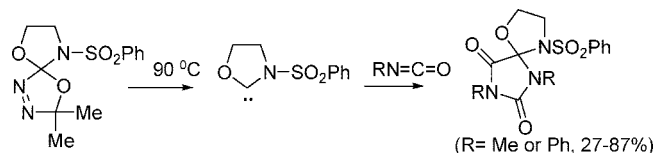


lar reactions with carbonyl groups<sup>47</sup> (Scheme 22<sup>47b</sup>) have afforded some novel products, **30** and **31**.

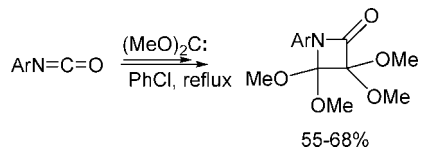
**4. Reactions with Thiocarbonyl Compounds.** Thiocarbonyl groups<sup>48</sup> also react with DMC, Schemes 23<sup>48a</sup> and 24.<sup>48e</sup> Isolation of **32**, a 2:1 adduct, Scheme 23, was surprising and suggested the operation of a polar effect to enhance the electrophilicity of the thiocarbonyl carbon that reacted to form it. Ring expansion (Scheme 23) or insertion of DMC (Scheme 24) is most easily understood in terms of a zwitterionic intermediate in which migration of a neighboring group to the positive site of the zwitterion (C<sup>+</sup>(OMe)<sub>2</sub>) occurs.

**5. Reactions with Imines and Cumulenes.** DMC reacts with iminyl double bonds in the 1,2-sense (with subsequent rearrangement),<sup>49</sup> as well as in the 1,4-sense.<sup>50</sup> Reactions of similar carbenes with isocyanates<sup>51</sup> are illustrated in Schemes 25,<sup>51</sup> 26<sup>51b</sup> and 27.<sup>51c</sup> In Schemes 25–27, for example, a possible intermediate is an α-lactam that reacts with another mole of isocyanate (or carbene). The mechanisms remain to be investigated. Scheme 27 is particularly intriguing because formation of a four-membered ring could indicate reaction of

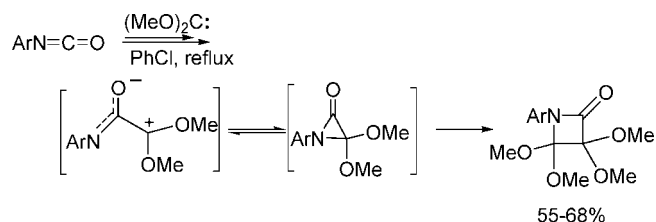
## SCHEME 26



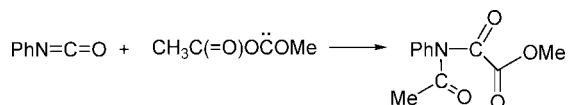
## SCHEME 27



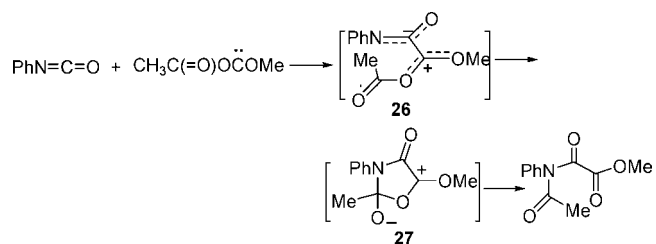
## SCHEME 28



## SCHEME 29



## SCHEME 30

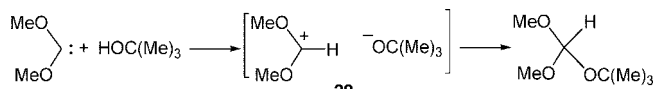


a zwitterionic intermediate (or a dimethoxy- $\alpha$ -lactam) with DMC, Scheme 28.<sup>51c</sup> A similar product was not reported in a study of the reaction of phenyl isocyanate with DMC from the bicyclic precursor of Scheme 2,<sup>51a</sup> suggesting that reactions of DMC may be very dependent on reaction conditions.

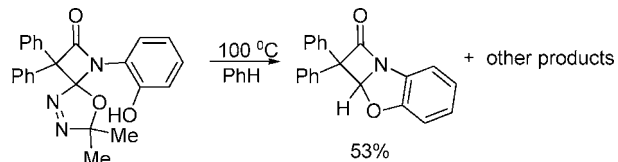
Acetoxy(methoxy)carbene also reacts with isocyanates, Scheme 29.<sup>6a</sup> The mechanism, Scheme 30, probably involves **26** as an intermediate that appears to be set up for acetyl transfer by a nucleophilic substitution mechanism. Although that mechanism fits the products, the intermediate that follows next (**27**) is not necessarily stabilized sufficiently in benzene. The mechanism remains to be established. DMC was also shown to react with some diketenes.<sup>52</sup>

**6. Reaction with Alcohols and Phenols.** *t*-Butyl alcohol or phenols have been used to demonstrate that a nucleophilic

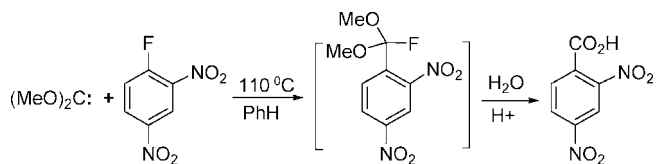
## SCHEME 31



## SCHEME 32



## SCHEME 33



carbene is formed by thermolysis of an oxadiazole.<sup>9,14a</sup> Alcohols and phenols presumably protonate the nucleophilic carbene to afford an ion-pair intermediate<sup>53</sup> (**28**, for example) that collapses to an orthoformate, Scheme 31. An intramolecular analogue has been reported, Scheme 32.<sup>14b</sup>

**7. Miscellaneous.** Substitution, characteristic of nucleophiles, has been observed with Sanger's reagent as substrate, Scheme 33.<sup>54</sup>

The schemes above are only a few examples of heteroatom-substituted carbene reactions. Readers looking for other reactions should consult the references cited or could use a search engine, such as Scifinder, to search under information, structures, or authors' names. Some preparations have not been published in detail, and many mechanisms have not been established, but the application procedure is generally very simple.

## Summary and Outlook

Although many reactions and properties of heteroatom-substituted carbenes, derived primarily through thermolysis of appropriate oxadiazoles, have been studied, it is clear that only the surface is scratched and that many more uses of those versatile reagents will be forthcoming. The author hopes that this Account will inspire chemists worldwide to think of and to try new applications.

*The efforts of many of Warkentin's skilled co-workers, whose names appear in some of the references, are gratefully acknowledged. Financial support was provided by the Natural Sciences and Engineering Research Council of Canada.*

## BIOGRAPHICAL INFORMATION

**John Warkentin**, currently Professor Emeritus at McMaster University, began his university training at the University of Manitoba, where he worked with Professor G. E. Dunn. Following that, he obtained a Ph. D. from Iowa State College, where he worked with Professor G. S. Hammond. Next there came a postdoctoral fellowship (PDF) at the California Institute of Technology, again with Hammond, and then a second PDF, with Professor P. D. Bartlett at Harvard University. He joined the Chemistry Department at McMaster University in 1960. During his career at McMaster, he spent sabbatical leaves at the University of California, San Diego, the Australian National University, the National Research Council of Canada, Ottawa, and The Ohio State University. The sponsorship of Deutscher Akademischer Austausch Dienst (DAAD) took him to the Georg August University in Göttingen. He was a member of the Chemistry Grants Selection Committee of the Natural Sciences and Engineering Research Council of Canada for two years and its chairman for one year. He was also Departmental Chairman at McMaster for three years. Initially his research was in the general area of Physical Organic Chemistry, including free radicals, but lately it has been concentrated in the chemistry of nucleophilic carbenes.

## REFERENCES

- (a) Hoffmann, R. W.; Häuser, H. Thermische Spaltung von 7,7-Dimethoxybicycloheptadien-[2.2.1]-derivaten, Ein Weg zum Tetramethoxy-athylen. *Tetrahedron Lett.* **1964**, 197–201. (b) Lemal, D. M.; Gosselink, E. P.; Ault, A. Fragmentation of Substituted Norbornadienone Ketals. *Tetrahedron Lett.* **1964**, 579–584.
- (a) Hoffmann, R. W.; Häuser, H. Tetramethoxyethylene. I. Thermal Cleavage of 7,7-Di-methoxynorbornadiene Derivatives. *Tetrahedron* **1965**, *21*, 891–902. (b) Hoffmann, R. W.; Reiffen, M. Über das Nucleophile Verhalten von Dimethoxycarbene. *Chem. Ber.* **1976**, *109*, 2565–2571.
- Moss, R. A. Diazirines: Carbene Precursors Par Excellence. *Acc. Chem. Res.* **2006**, *39*, 267–272.
- El-Saidi, M.; Kassam, K.; Pole, D. L.; Tadey, T.; Warkentin, J. 2,2-Dialkoxy- $\Delta^3$ -1,3,4-oxadiazolines: Convenient Thermal Sources of Dialkoxycarbenes. *J. Am. Chem. Soc.* **1992**, *114*, 8751–8752.
- Pole, D. L.; Warkentin, J. C-O Bond Insertion in the Reaction of Dialkoxycarbenes with Anhydrides. *Liebigs Ann.* **1995**, 1907–1914.
- (a) Sokol, W.; Warkentin, J. Synthesis and Thermolysis Rate Constants of Diastereomeric Oxadiazoline Sources of Acetoxy(methoxy)carbene. Reaction of Acetoxy(methoxy)carbene with Isocyanates. *Can. J. Chem.* **2006**, *84*, 927–933. (b) Czardybon, W.; Sokol, W.; Warkentin, J.; Werstiuk, N. H. 6,7-Diaza-1-methoxy-5-methyl-2,8-dioxabicyclo[3.2.1]oct-6-ene. An Unstable Bicyclic Precursor of a Dioxo Carbonyl Ylide and Carbenes by Ylide Ring Opening. *J. Phys. Org. Chem.* **2008**, *21*, 41–46.
- de Meijere, A.; Kozhushkov, S. I.; Yufit, D. S.; Boese, R.; Haumann, T.; Pole, D. L.; Sharma, P. K.; Warkentin, J. Unprecedented Addition of Dialkoxycarbenes to Tetrasubstituted Alkenes: Bicyclopropylidene and 2-Chlorocyclopropylideneacetate. *Liebigs Ann.* **1996**, 601–612.
- Kassam, K.; Pole, D. L.; El-Saidi, M.; Warkentin, J. New Convenient Source of Precursors of Dioxycarbenes. *J. Am. Chem. Soc.* **1994**, *116*, 1161–1162.
- Zhou, H.; Mloston, G.; Warkentin, J. New Thermal Source of Dimethoxycarbene Leading to Zwitterionic Intermediates and 2:1 Stoichiometry in Reaction with Electrophilic Alkenes. *Org. Lett.* **2005**, *7*, 487–489. Erratum: *Org. Lett.* **2008**, *10*, 1323.
- (a) Lu, X.; Reid, D. L.; Warkentin, J. Diaryloxycarbenes from Oxadiazolines. *Can. J. Chem.* **2001**, *79*, 319–327. (b) Lu, X.; Warkentin, J. Mechanism of *Ipsa* Aromatic Substitution in Reaction of Aryloxymethoxycarbenes and Diaryloxycarbenes with DMAD. *Can. J. Chem.* **2001**, *79*, 364–369.
- (a) Warkentin, J. Diamino-, Amino(oxy)-, Dioxo-, Amino(thio)-, Oxy(thio)-, and Dithiocarbenes. *Advances in Carbene Chemistry*; Brinker, U. H., Ed.; JAI Press: Greenwich, CT, 1998; Vol. 2, 245–295. (b) Warkentin, J.  $\Delta^3$ -1,3,4-Oxadiazolines. Versatile Sources of Reactive Intermediates. *J. Chem. Soc., Perkin Trans. 1* **2000**, 2161–2169.
- Er, H.-T.; Pole, D. L.; Warkentin, J. (Alkylthio) and (Phenylthio)methoxycarbenes from Oxadiazolines. *Can. J. Chem.* **1996**, *74*, 1480–1489.
- (a) Schreiner, P. R.; Reisenauer, H. P.; Romanski, J.; Mloston, G. [1,3]Dithian-2-ylidene. *Angew. Chem., Int. Ed.* **2006**, *45*, 3989–3992. (b) Rigby, J. H.; Sidique, S. Total Synthesis of ( $\pm$ )-Phenserine via [4 + 1] Cyclization of a Bis(alkylthio)carbene and an Indole Isocyanate. *Org. Lett.* **2007**, *9*, 1219–1221. (c) Rigby, J. H.; Burke, P. J. Synthesis of Highly Substituted Indole Alkaloid Species via [4 + 1] Cyclization of Nucleophilic Carbenes and Indole Isocyanates. *Heterocycles* **2006**, *67*, 643–653. (d) Rigby, J. H.; Wang, Z. Synthesis of Highly Substituted Cyclopentenones via the [4 + 1] Cycloaddition of Nucleophilic Carbenes and Vinyl Ketenes. *Org. Lett.* **2003**, *5*, 263–264. (e) Rigby, J. H.; Neale, N. A.; Schlegel, H. B. Mechanistic Studies on the Reactions of Bis(alkylthio)carbenes with Vinyl Isocyanates. *Heterocycles* **2002**, *5*, 105–113. (f) Rigby, J. H.; Wang, Z. [4 + 1] Cycloaddition of N-Heterocyclic Carbenes with Vinyl Isocyanates. *Org. Lett.* **2002**, *4*, 4289–4291. (g) Rigby, J. H.; Dong, W. [4 + 1] Cycloaddition of Bis(alkylthio)carbenes with Vinyl Isocyanates. Total Synthesis of ( $\pm$ )-Mesembrine. *Org. Lett.* **2000**, *2*, 1673–1675. (h) Rigby, J. H.; Laurent, S.; Dong, W.; Danca, M. D. Bis(alkylthio)carbenes as Novel Reagents for Organic Synthesis. *Tetrahedron* **2000**, *56*, 10101–10111. (i) Rigby, J. H.; Danca, M. D. Rapid Construction of Isatin Derivatives via Addition of Bis(alkylthio)carbenes to Aryl Isocyanates. *Tetrahedron Lett.* **1999**, *40*, 6891–6894. (j) Rigby, J. H.; Laurent, S. Nucleophilic Carbenes in Synthesis. [1 + 4] Cycloaddition of Bis(alkylthio)carbenes with Vinyl Isocyanates. *J. Org. Chem.* **1999**, *64*, 1766–1767.
- (a) Couture, P.; Warkentin, J. Spiro-fused 2-Alkoxy-2-amino- $\Delta^3$ -1,3,4-oxadiazolines. Synthesis and Thermolysis to Corresponding Aminoxy-carbenes. *Can. J. Chem.* **1997**, *75*, 1264–1280. (b) Couture, P.; Warkentin, J. A Benzo-fused Oxapenem from a  $\beta$ -Lactam-4-ylidene. *Can. J. Chem.* **1998**, *76*, 241–244. (c) Couture, P.; Terlouw, J. K.; Warkentin, J. 2-Alkoxy-2-amino- $\Delta^3$ -1,3,4-oxadiazolines as Novel Sources of Alkoxyaminocarbenes. *J. Am. Chem. Soc.* **1996**, *118*, 4214–4215.
- (a) Czardybon, W.; Klys, A.; Warkentin, J.; Werstiuk, N. H. 2-Acetoxy-2-methoxy-5,5-dimethyl- $\Delta^3$ -1,3,4-oxadiazoline and Acetoxy(methoxy)carbene. *Can. J. Chem.* **2003**, *81*, 1438–1442. (b) Klys, A.; Czardybon, W.; Warkentin, J.; Werstiuk, N. H. Synthesis and Thermolysis of a Spiro-fused Oxadiazoline-Evidence for Sequential Formation of Carbene and Oxirane Intermediates, and for Oxirane Dimerization. *Can. J. Chem.* **2004**, *82*, 1769–1773. (c) Czardybon, W.; Warkentin, J.; Werstiuk, N. H. Density Functional Theory Computational Study on the Thermal Cycloreversion of 2-Acetoxy-2-methoxy-5,5-dimethyl- $\Delta^3$ -1,3,4-oxadiazoline: Evidence for a Carbonyl Ylide Intermediate. *J. Org. Chem.* **2005**, *70*, 8431–8436.
- Merkley, N.; Warkentin, J. Thermolysis of a Spiro-fused Oxadiazoline. The Carbonyl Ylide/Cyclic Carbene/Diradical Sequence. *Can. J. Chem.* **2002**, *80*, 1187–1195.
- Pezacki, J. P.; Wagner, B. D.; Lew, C. S. Q.; Warkentin, J.; Luszyk, J.  $\Delta^3$ -1,3,4-Oxadiazolines: Photochemical Precursors to *sec*-Alkanediazonium Ions in Acidic Solution. *J. Am. Chem. Soc.* **1997**, *119*, 1789–1790.
- Rajagopalan, P.; Advani, B. G. 1,3-Cycloaddition Reactions of Carbonyl Ylides from Oxadiazolines. *Tetrahedron Lett.* **1967**, 2689–2695.
- Hoffmann, R. W.; Luthardt, H. J. Thermolysis and Photolysis of  $\Delta^3$ -1,3,4-Oxadiazolines. *Chem. Ber.* **1968**, *101*, 3861–3871.
- Moss, R. A.; Wlostowski, M.; Shen, S.; Krogh-Jespersen, K.; Matro, A. Dimethoxycarbene: Direct Observation of an Archetypal Nucleophilic Carbene. *J. Am. Chem. Soc.* **1988**, *110*, 4443–4444.
- Muchall, H. M.; Werstiuk, N. H.; Choudhury, B.; Ma, J.; Warkentin, J.; Pezacki, J. P. Thermolysis of 2,2-dimethoxy-5,5-dimethyl- $\Delta^3$ -1,3,4-oxadiazoline studied with Photoelectron Spectroscopy. He(I) Photoelectron Spectrum of Dimethoxycarbene. *Can. J. Chem.* **1998**, *76*, 238–241.
- Reisenauer, H. P.; Romanski, J.; Mloston, G.; Schreiner, P. R. Dimethoxycarbene: Conformational Analysis of a Reactive Intermediate. *Eur. J. Org. Chem.* **2006**, 4813–4818.
- Du, X.-M.; Fan, H.; Goodman, J. L.; Kesselmayr, M. A.; Krogh-Jespersen, K.; LaVilla, J. A.; Moss, R. A.; Shen, S.; Sheridan, R. S. Reactions of Dimethoxycarbene and Fluroromethoxycarbene with Hydroxyl Compounds. Absolute Rate Constants and the Heat of Formation of Dimethoxycarbene. *J. Am. Chem. Soc.* **1990**, *112*, 1920–1926.
- Czardybon, W.; Warkentin, J.; Werstiuk, N. H. Computational Study of the Thermal Rearrangement of Acetoxy(methoxy)carbene. *J. Phys. Org. Chem.* **2005**, *18*, 486–490.
- Guthrie, J. P.; More-O'Ferrall, R. A.; O'Donoghue, A. C.; Waghorne, W. E.; Zrinski, I. Estimation of a pKa for Protonated Dimethoxycarbene. *J. Phys. Org. Chem.* **2003**, *16*, 582–587.
- Pezacki, J. P. Normal Acid/Base Behaviour in Proton Transfer Reactions to Alkoxy-substituted Carbenes; Estimates for Intrinsic Barriers to Reaction and pKa Values. *Can. J. Chem.* **1999**, *77*, 1230–1240.

- 27 Suh, D.; Pole, D. L.; Warkentin, J.; Terlouw, J. K. Intramolecular 1,2-Alkyl Shifts in Unsymmetric Dialkoxycarbenes Studied by Very Low Vapour Pressure (VLVP) Pyrolysis-mass Spectrometry. *Can. J. Chem.* **1996**, *74*, 544–558.
- 28 Merkley, N.; El-Saidi, M.; Warkentin, J. Radicals from Fragmentation of Benzyloxy(methoxy)carbenes in Solution. *Can. J. Chem.* **2000**, *78*, 356–361.
- 29 Merkley, N.; Venneri, P. C.; Warkentin, J. Cyclopropanation of Benzyldenemalononitrile with Dialkoxycarbenes and Free Radical Rearrangement of the Cyclopropanes. *Can. J. Chem.* **2001**, *79*, 312–318.
- 30 Merkley, N.; Warkentin, J. Benzyloxy(4-substitutedbenzyloxy)carbenes. Generation from Oxadiazolines and Fragmentation to Radical Pairs in Solution. *Can. J. Chem.* **2000**, *78*, 942–949.
- 31 Warkentin, J. Intra- and Intermolecular Reactions of Nucleophilic Carbenes. *Macromol. Symp.* **1998**, *134*, 167–176.
- 32 Moss, R. A.; Young, C. M.; Perez, L. A.; Krogh-Jespersen, K. Carbenic Philicity: 6,6-Dimethylfulvene as an Indicator Substrate. *J. Am. Chem. Soc.* **1981**, *103*, 2413–2415.
- 33 Butler, D. N.; Halton, B.; Warkentin, J.; Warriner, R. N. Synthesis and Opening of a Ring Fused Bicyclo[2.1.0]pentan-5-one Acetal. *Aust. J. Chem.* **2000**, *53*, 561–566.
- 34 Sliwinska, A.; Czardybon, W.; Warkentin, J. Zwitterion from a Cyclopropane with Geminal Donor and Acceptor Groups. *Org. Lett.* **2007**, *9*, 695–698.
- 35 Lemal, D. M.; Gosselink, E. P.; McGregor, S. D. Thermal Decomposition of Substituted Norbornadienone Ketals. *J. Am. Chem. Soc.* **1966**, *88*, 582–600.
- 36 Moss, R. A.; Huselton, J. K. Dimethoxycarbene: Stereospecificity in the Addition of a Nucleophilic Carbene to  $\beta$ -Deuteriostyrenes. *J. Chem. Soc., Chem. Commun.* **1976**, 950–951.
- 37 (a) Howe, N. E.; Yankee, E. W.; Cram, D. J. Stereochemistry. XLV. Zwitterionic Transition States in Epimerization Reactions of Substituted Cyclopropanes. *J. Am. Chem. Soc.* **1973**, *95*, 4230–4237. (b) Chmurny, A. B.; Cram, D. J. Studies in Stereochemistry. Singlet Diradical Transition States in Epimerization Reactions of Cyclopropanes. *J. Am. Chem. Soc.* **1973**, *95*, 4237–4244.
- 38 Buchert, M.; Reissig, H.-U. Rearrangement of Donor-Acceptor-Substituted Vinylcyclopropanes to Functionalized Cyclopentene Derivatives. Evidence for Zwitterionic Intermediates. *Liebigs Ann.* **1996**, 2007–2013.
- 39 (a) Nair, V.; Beneesh, P. B.; Sreekumar, V.; Bindu, S.; Menon, R. S.; Deepthi, A. The Multicomponent Reaction of Dimethoxycarbene, Dimethylbutylenedioate and Electrophilic Styrenes: An Unprecedented Synthesis of Highly Substituted Cyclopentenone Acetals. *Tetrahedron Lett.* **2005**, *46*, 201–203. (b) Nair, V.; Bindu, S.; Sreekumar, V.; Balagopal, L. Novel Dipolar Cycloaddition Reactions of Zwitterionic Species Generated from Dimethoxycarbene and Dimethyl Acetylenedicarboxylate with Carbonyl Compounds: Facile Synthesis of Dihydrofuran Derivatives. *Synthesis* **2003**, 1446–1456. (c) Nair, V.; Bindu, S.; Balagopal, L. A Novel Multicomponent Reaction of Dimethoxycarbene and DMAD with Aldehydes and Quinones: Facile Synthesis of Dihydrofuran Derivatives. *Tetrahedron Lett.* **2001**, *42*, 2043–2044.
- 40 Nair, V.; Deepthi, A.; Poonoth, M.; Santhamma, B.; Vellalath, S.; Babu, B. P.; Mohan, R.; Suresh, E. Reaction of Dimethoxycarbene-DMAD Zwitterion with 1,2-Diones and Anhydrides: A Novel Synthesis of Highly Substituted Dihydrofurans and Spirodihydrofurans. *J. Org. Chem.* **2006**, *71*, 2313–2319.
- 41 Lu, X.; Warkentin, J. Novel Products from Thermolysis of 5,5-Dimethyl-2,2-diphenoxy Oxadiazoline in the Presence of DMAD. *Org. Lett.* **2000**, *2*, 3501–3503. Erratum: *Org. Lett.* **2001**, *3*, 143.
- 42 (a) Kassam, K.; Warkentin, J. Thermolysis of 2-(3-Butyn-1-oxy)-2-methoxy- $\Delta^3$ -1,3,4-oxadiazoline in Solution. A Remarkable Cascade of Carbene and Other Reactions. *J. Org. Chem.* **1994**, *59*, 5071–5075. (b) Kassam, K.; Warkentin, J. Reactions of Dialkoxycarbenes with Tethered Triple Bonds to form Heterocyclic Compounds. *Can. J. Chem.* **1997**, *75*, 120–128. (c) Kassam, K.; Venneri, P. C.; Warkentin, J. Reactions of Alkoxyaryloxy-carbenes with Tethered Triple Bonds A New Synthesis of Substituted Benzofurans. *Can. J. Chem.* **1997**, *75*, 1256–1263.
- 43 (a) Spino, C.; Rezaei, H.; Dupont-Gaudet, K.; Bélanger, F. Inter- and Intramolecular [4 + 1]-Cycloadditions between Electron-Poor Dienes and Electron-Rich Carbenes. *J. Am. Chem. Soc.* **2004**, *126*, 9926–9927. (b) Boisvert, L.; Beaumier, F.; Spino, C. Evidence for a Concerted [4 + 1]-Cycloaddition between Electro-Rich Carbenes and Electron-Deficient Dienes. *Org. Lett.* **2007**, *9*, 5361–5363.
- 44 González, R.; Wudl, F.; Pole, D. L.; Sharma, P. K.; Warkentin, J. An Unusual Addition-Rearrangement of a Dialkoxycarbene to C60; Exclusion of Methanofullerene Products. *J. Org. Chem.* **1996**, *61*, 5837–5839.
- 45 Lilienblum, W.; Hoffmann, R. W. Carbene reactions, XI. Addition of dimethoxycarbene to dienes. *Chem. Ber.* **1977**, *110*, 3405–3409.
- 46 Pole, D. L.; Warkentin, J. Formation and Rearrangement of a 2,2-Dimethoxyoxirane from Dimethoxycarbene and Fluoren-9-one. *J. Org. Chem.* **1997**, *62*, 4065–4067.
- 47 (a) Romanski, J.; Mloston, G.; Heimgartner, H. Reactions of Polycyclic Ketones with Dimethoxycarbene; a Convenient Route for a 'One-Pot' Preparation of Some  $\alpha$ -Hydroxycarboxylic Acid Esters. *Helv. Chim. Acta* **2007**, *90*, 1279–1288. (b) Dawid, M.; Warkentin, J. Intramolecular Reactions of Dialkoxycarbenes with a Carbonyl Group. *Can. J. Chem.* **2003**, *81*, 598–606. (c) Dawid, M.; Venneri, P. C.; Warkentin, J. Epoxide of a Ketene Acetal. The First 2,2-Dialkoxyoxirane to be Isolated. *Can. J. Chem.* **2001**, *79*, 110–113. Erratum: *Can. J. Chem.* **2001**, *79*, 1294. (d) Venneri, P. C.; Warkentin, J. Reactions of Dimethoxycarbene with Strained Cyclic Carbonyl Compounds. *Can. J. Chem.* **2000**, *78*, 1194–1203 (ref 17c, page 1202, should read *J. Am. Chem. Soc.* **1998**, *120*, 3664).
- 48 (a) Dawid, M.; Reid, D. L.; Mloston, G.; Warkentin, J. Reactions of Dimethoxycarbene with Thiocarbonyl Compounds. *Can. J. Chem.* **2003**, *81*, 1025–1028. (b) Dawid, M.; Reid, D. L.; Warkentin, J.; Mloston, G. Reactions of Dimethoxycarbene with Carbon-Sulfur Double Bonds. *J. Phys. Org. Chem.* **2005**, *18*, 86–89. (c) Dawid, M.; Mloston, G.; Warkentin, J. Relative Reactivities of Carbonyl and Thiocarbonyl Groups toward Dimethoxycarbene: Two New Dimethoxythiiranes. *Chem.—Eur. J.* **2002**, *8*, 2184–2187. (d) Dawid, M.; Mloston, G.; Warkentin, J. The First 2,2-Dialkoxythiirane. *Org. Lett.* **2001**, *3*, 2455–2456. (e) Erian, A. W.; Reid, D. L.; Warkentin, J. Reactions of Dimethoxycarbene with Xanthates. *J. Sulfur Chem.* **2005**, *26*, 203–209.
- 49 (a) Mloston, G.; Heimgartner, H. The First Reaction of Dimethoxycarbene with an Imine Moiety. *Helv. Chim. Acta* **2007**, *90*, 1758–1764. (b) Mloston, G.; Warkentin, J.; Linden, A.; Heimgartner, H. Reactions of Dimethoxycarbene with N-Tosylated Imines. *Helv. Chim. Acta* **2007**, *90*, 2024–2036.
- 50 Hoffmann, R. W.; Steinbach, K.; Lilienblum, W. Addition von Dimethoxycarben an Heterodiene. *Chem. Ber.* **1976**, *109*, 1759–1768.
- 51 (a) Hoffmann, R. W.; Steinbach, K.; Dittrich, B. Addition von Dimethoxycarben an Isocyanate und Isothiocyanate. *Chem. Ber.* **1973**, *106*, 2174–2184. (b) Couture, P.; Warkentin, J. Chemistry of Cyclic Aminooxycarbenes. *Can. J. Chem.* **1997**, *75*, 1281–1294. (c) Rigby, J. H.; Brouet, J.-C.; Burke, P. J.; Rohach, S.; Sidiq, S.; Heeg, M. J. New Entry into  $\beta$ -Lactams via Reaction of Dimethoxycarbene with Isocyanates. *Org. Lett.* **2006**, *8*, 3121–3123.
- 52 Colomvakos, J. D.; Egle, I.; Ma, J.; Pole, D. L.; Tidwell, T. T.; Warkentin, J. [2 + 2], [4 + 1], and [4 + 2] Cycloaddition Reactions of Silylated Bisketenes. *J. Org. Chem.* **1996**, *61*, 9522–9527.
- 53 Kirmse, W. Carbenes and the OH Bond. *Advances in Carbene Chemistry*; Brinker, U. H., Ed.; JAI Press: Greenwich, CT, 1994, Vol. 1, pp 1–57.
- 54 Ross, J. P.; Couture, P.; Warkentin, J. Nucleophilic Aromatic Substitution with Dialkoxycarbenes. *Can. J. Chem.* **1997**, *75*, 1331–1335.