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New Thermal Source of Dimethoxycarbene Leading to Zwitterionic Intermediates and 2:1 Stoichiometry in Reaction with Electrophilic Alkenes

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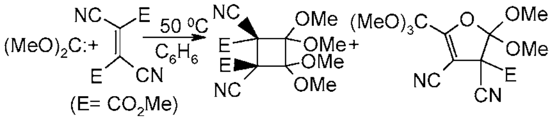
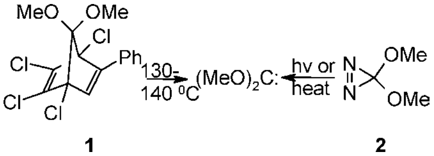
ABSTRACT



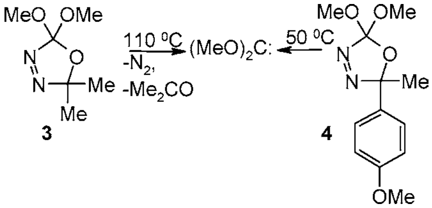
At 50 °C, dimethyl dicyanofumarate and maleate react with 2 equiv of dimethoxycarbene to generate the products shown.

Dimethoxycarbene (DMC), studied by Hoffmann and his group[1] and by Lemal,[2] was generated at 130 °C by thermolysis of the norbornadienone ketal **1**, Scheme 1. Moss's group[3] used thermolysis (15−50 °C) or photolysis of 3,3-dimethoxydiazirine **2**, Scheme 1. The Hoffmann method suffers from the high temperature required and the Moss approach is not very useful for synthetic applications, because the explosive diazirines are generally available only as dilute solutions in a solvent such as pentane.

Scheme 1



Scheme 2



2,5-Dihydro-2,2-dimethoxy-5,5-dimethyl-1,3,4-oxadiazole (also known as 2,2-dimethoxy-5,5-dimethyl-Δ^3-1,3,4-oxadiazoline) (**3**), was introduced in 1992[4,5] as a shelf-stable, thermal source of DMC (Scheme 2). Dihydrodialkoxyoxadiazoles have since been used as dialkoxycarbene sources by Diederich,[6] Rigby,[7] Werstiuk,[8] Terlouw,[9] Nair,[10] and

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[1] (a) Hoffmann, R. W.; Häuser, H. *Tetrahedron Lett.* **1964**, 197. (b) Hoffmann, R. W. *Acc. Chem. Res.* **1985**, *18*, 248 and references therein.

[2] Lemal, D. M.; Gosselink, E. P.; McGregor, S. D. *J. Am. Chem. Soc.* **1966**, *88*, 582.

[3] Moss, R. A.; Wlostowski, M.; Shen, S.; Krogh-Jespersen, K.; Matro, A. *J. Am. Chem. Soc.* **1988**, *110*, 4443.

[4] El-Saidi, M.; Kassam, K.; Pole, D. L.; Tadey, T.; Warkentin, J. *J. Am. Chem. Soc.* **1992**, *114*, 8751.

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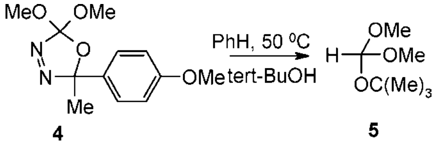
Spino,[11] for example. DMC is usually generated by heating **3** at 110 °C, as a solution in benzene in a sealed tube.

We now report that 2,5-dihydro-2,2-dimethoxy-5-methyl-5-(*p*-methoxy)phenyl-1,3,4-oxadiazole (**4**) is an excellent alternative thermal source of DMC in benzene solution, at 40−50 °C (Scheme 2), the lower temperature permitting the isolation of products that might not survive at 110 °C.

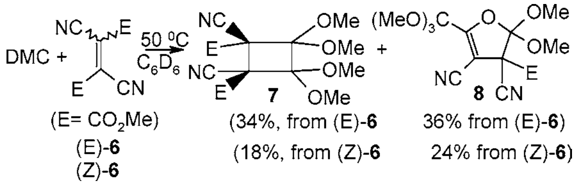
Thermolysis of **4** at 50 °C, in C_6D_6 containing *tert*-butylbenzene as an internal standard, was followed by ^{1}H NMR spectroscopy. A six-point plot of $\ln(I_{Me}/I_{tert-Bu})$ against time, where I_{Me} is the value of the integral from the C5 methyl group of **4** and $I_{tert-Bu}$ is the analogous value for the *tert*-butyl group of the internal standard, was linear and gave $k_4 = 1.8 \times 10^{-5}\ s^{-1}$, with $r^2 = 0.998$. An analogous thermolysis with *tert*-butyl alcohol present gave *tert*-butyl dimethyl orthoformate (**5**) in 73% yield (Scheme 3), indicating that DMC had been generated. The integral from the aromatic ^{1}H NMR signals of 4-methoxyacetophenone was 4 times that of the orthoformyl ^{1}H signal from **5**, indicating that the ketone and DMC were formed in 1:1 ratio.

Scheme 3



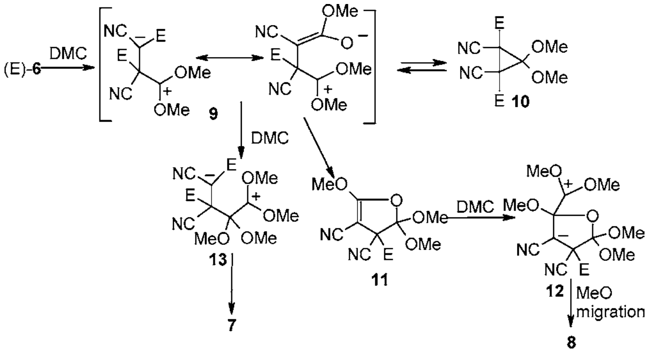
Reaction of DMC from **4** with dimethyl dicyanofumarate ((*E*)-**6**) and dimethyl dicyanomaleate ((*Z*)-**6**) were also run in benzene, in which (*E*)-**6** is sparingly soluble. We reasoned that the thermolysis of **4** is slow enough to prevent dimerization of DMC (second-order in DMC) if an alternative reaction is available for the carbene and that solid/solution equilibrium involving (*E*)-**6** would probably be maintained, providing a low steady-state concentration of the alkene for reaction with DMC. That choice of solvent turned out to be advantageous as discussed below. Scheme 4 illustrates the products from reaction of DMC with (*E*)-**6** and (*Z*)-**6**. The structures of **7** and **8** were determined by means of X-ray diffraction.

Scheme 4



It is clear that there must be an intermediate such as **9** in the reactions with DMC, possibly as illustrated in Scheme 5 for the case of (*E*)-**6**. The intermediate may cyclize reversibly, although there is no evidence for **10**. However, there is a precedent for thermal ring opening of a cyclopropane with two methoxy groups at one site and one ester substituent.[12] Reaction of **9** with DMC affords **13**, which cyclizes to **7**. Intermediate **9** is a delocalized system and can also cyclize to dihydrofuran **11**, which reacts with DMC to afford intermediate **12**. The latter rearranges by methoxy migration to afford **8**. The existence of zwitterionic intermediates during 1,3-dipolar cycloadditions of (*E*)-**6** and (*Z*)-**6** with electron-rich thiocarbonyl ylides is now well established.[13]

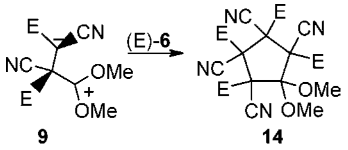
Scheme 5



The fact that (*Z*)-6 did not afford isolable geometric isomers of **7** confirms a stepwise mechanism and indicates that rotation in the zwitterionic intermediate from (*Z*)-**6** is fast.

Reaction of (*E*)-**6** with DMC in 1,4-dioxane, in which (*E*)-**6** is soluble, gave a very complex mixture of products, and their separation was not attempted. Most likely, intermediates such as **9** undergo cycloadditions with (*E*)-**6**, which is itself an active dipolarophile. Scheme 6 shows that such a reaction alone could account for many of the methoxy signals because the adducts such as **14** have four asymmetric centers.

Scheme 6



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(13) (a) Giera, H.; Huisgen, R.; Langhals, E.; Polborn, K. *Helv. Chim. Acta* **2002**, *85*, 1523. (b) Huisgen, R.; Mloston, G.; Giera, H.; Langhals, E. *Tetrahedron* **2002**, *58*, 507.

Compound (*Z*)-**6**, which is more soluble than (*E*)-**6** in benzene at 50 °C, also gave a complex mixture of compounds from which only the main components, **7** and **8**, were obtained. Although geometric isomers of **7** and **8** may have been present in small amounts in the unresolved mixture that remained (more than 14 methoxy signals), none were isolable.

To check whether DMC from **3** could also afford **7** and **8**, **3** was thermolyzed at 110 °C in benzene in the presence of (*E*)-**6**. Under these conditions, (*E*)-**6** was completely dissolved (98 mg in 2 mL). The solution turned black in less than 1 h, and workup after 12 h gave a very complex mixture of products (more than 15 MeO signals in the ^{1}H NMR spectrum of the crude), illustrating that temperature and concentration play a decisive role. The novel reactions between (*E*)-**6** (or (*Z*)-**6**) and DMC are available with DMC from **4** but not from **3**.

Reactions of other electrophilic alkenes with DMC are currently under investigation.

Acknowledgment. The work of Professor Jim Britten, who determined the crystal and molecular structures of **7** and **8**, is greatly appreciated. J.W. and H.Z. gratefully acknowledge the continued financial support of NSERC. G.M. thanks the Polish State Committee for Scientific Research for financial support (Grant 3 T09A 046 25).

Supporting Information Available: Detailed experimental procedures and ORTEP renditions of **7** and **8**. This material is available free of charge via the Internet at http://pubs.acs.org.

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