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Reactions of Dimethoxycarbene with Dimethyl 2,3-Dicyanomaleate and Fumarate

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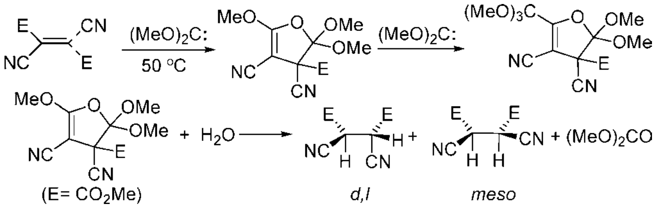
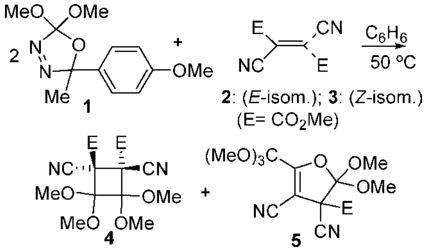
ABSTRACT



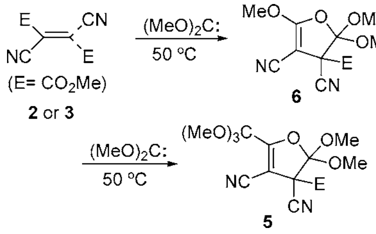
Dimethoxycarbene, in 2-fold or larger excess, reacts with dimethyl 2,3-dicyanomaleate and fumarate to afford an unstable dihydrofuran 1:1 adduct that was shown to react further with the carbene to afford a 2:1 adduct reported previously. In an astonishing process, the dihydrofuran reacts with water to afford a mixture of (*d,l* and *meso*) dimethyl 2,3-dicyanosuccinates in which both hydrogen atoms of water were used to hydrogenate a C═C bond.

Dimethyl 2,3-dicyanoethenes (**2** and **3**) are very electrophilic alkenes and react, as expected, with the nucleophilic dimethoxycarbene (DMC).[1] The products from 2 equiv or more of the carbene precursor (**1**) are a cyclobutane **4** and a dihydrofuran **5**, which is also a bis-orthoformate. Those products are not obviously related to the cyclopropane expected from initial cycloaddition of the carbene to either alkene, Scheme 1. We now report that the dihydrofuran **5** is derived from a very reactive dihydrofuran precursor (**6**) by reaction with DMC (Scheme 2). The latter dihydrofuran is exceedingly reactive toward moisture and reacts with water to hydrogenate a carbon−carbon double bond.

Scheme 1



Scheme 2



One possible source of the cyclobutane (**4**) is reaction of tetramethoxyethene, formed by a previously unrecognized partial decomposition of the carbene precursor **1**, and reaction of the carbene dimer with **2** or **3**, Scheme 3. Although dimethyl fumarate and dimethyl maleate afford both the *cis* and *trans* **4** (Scheme 3), the result in Scheme 1 is accounted

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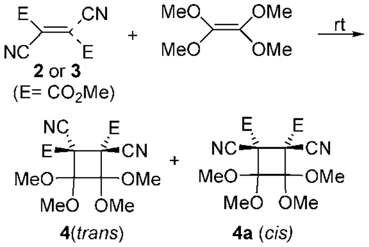
[1] Zhou, H.; Mloston, G.; Warkentin, J. *Org. Lett.* **2005**, *7*, 487.

10.1021/ol071143u CCC: $37.00

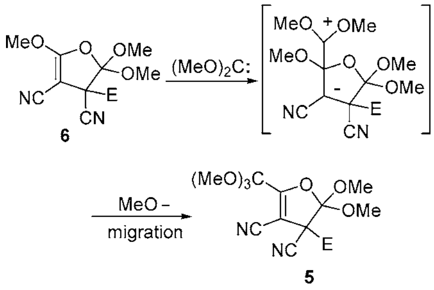
Scheme 3



for because the *cis* compound isomerizes to the *trans* isomer in benzene at 50 °C. Most reactions were carried out with **2**, which is more easily purified than **3**.

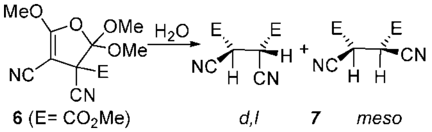
We had suggested earlier[1] that **5** could be derived from **6** by stepwise addition followed by ionic rearrangement, Scheme 4. The mechanism is convenient but not necessarily correct and there was no evidence for the intermediacy of **6**.

Scheme 4



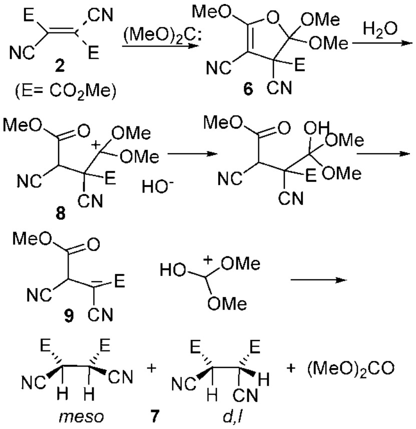
An implicit assumption was that **6** reacted rapidly with DMC; an assumption that we now recognize as incorrect. The reason for failure to observe **6**, which is an enediol and an orthoester at the same time, lies in its very high reactivity toward moisture, not in its high reactivity toward DMC. The reactivity of **6** toward moisture makes chromatographic purification impossible. We have now managed, with some difficulty, to isolate and to purify **6** enough to identify it beyond doubt.[2] It reacts with DMC at 50 °C to afford **5** as speculated earlier,[1] Scheme 4. It also reacts very readily with moisture, to afford a 1:1 mixture of *d,l* and *meso* dimethyl 2,3-dicyanosuccinates **7**,[3] which were not separated. The hydrolysis, which leads effectively to the hydrogenation of dimethyl 2,3-dicyanofumarate, is illustrated in Scheme 5.

Scheme 5



A potential mechanism for the novel process, which may involve the intermediacy of ion pairs **8** (**8** could be avoided if the first step with water is concerted) and **9** with dimethyl carbonate as coproduct, is suggested in Scheme 6. Dimethyl carbonate was a major component of the crude reaction product, as indicated by ^{1}H NMR spectroscopy with and without authentic dimethyl carbonate added.

Scheme 6



There are models of **6**, including compound **5** and others, that have the basic 5-membered enol orthoester ring structure of **6**[4] but none that are enediols and also cyclic orthoesters. None of them were reported to undergo the reaction with water that leads to the transfer of both hydrogen atoms of water to unsaturated carbon atoms. The special properties of **6** are, no doubt, responsible for the overall hydrogenation process. We are not aware of any precedent for hydrogenation of a C=C bond with water as the hydrogen donor.

The origin of **4** was particularly mysterious. It is, formally, the [2+2] adduct of **2** and the carbene dimer as already mentioned, Scheme 3. It was difficult to believe that DMC would dimerize in the presence of an electrophilic alkene such as **2**. DMC, obtained by thermolysis of dihydrooxadiazole **1**[1] at 50 °C, is formed with a rate constant of ca. 2×10^{-5} s^{-1}. Dimerization, which cannot occur with a rate constant that is larger than that for a diffusion-controlled reaction, is necessarily second order in [DMC] and cannot

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(2) A few minor impurities remain. Compound **6** was obtained as primary product by thermolysis of 1.3 equiv of the DMC source in benzene in the presence of fumarate **2** or maleate **3**, in a degassed, sealed tube at 50 °C for 24 h. Nearly pure **6** was isolated from the reaction mixture by washing with hexane to remove most of the *p*-methoxyacetophenone byproduct. Any attempt to prepare a pure sample of **6** led to its hydrolysis and formation of succinates **7**. The yield of the crude **6** exceeded 90%; ^{1}H NMR (600 MHz, $CDCl_3$) δ 3.50 (s, 3H), 3.68 (s, 3H), 3.91 (s, 3H), 4.14 (s, 3H); ^{13}C NMR (150.9 MHz, $CDCl_3$) δ 52.8, 53.5, 54.7, 59.0, 59.5, 59.8, 112.6, 113.4, 120.6, 162.8, 168.1; HRMS (CI, NH_3) *m/z* calcd for $C_{11}H_{13}N_2O_6$ $(M + H)^+$ 269.0774, found 269.0766.

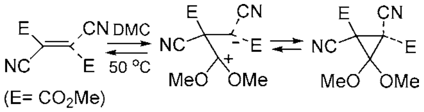
(3) A mixture of succinates **7** was obtained through attempts to purify dihydrofurane **6** on silica gel. Dense oil, yield 80%; ^{1}H NMR of the mixture of isomers in ca 1:1 ratio (500 MHz, $CDCl_3$) δ 3.921 (s, 6H), 3.929 (s, 6H), 4.24 (s, 2H), 4.29 (s, 2H); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 37.02, 37.11, 54.87, 54.94, 112.45, 112.62, 162.92, 163.03; HRMS (CI, NH_3) *m/z* calcd for $C_8H_9N_2O_4$ $(M + H)^+$ 197.0562, found 197.0563.

(4) For example: (a) Kesteleyn, B.; De Kimpe, N. *J. Org. Chem.* **2000**, *65*, 635. (b) Lebel, H.; Grenon, M. *Sci. Synth.* **2005**, *22*, 669. (c) Tidwell, T. T. *Sci. Synth.* **2006**, *23*, 391.

possibly compete with addition to the alkene unless the rate constant for addition of the carbene to the alkene is actually small or until the concentration of the alkene has become very small. Once the alkene is depleted, the carbene can dimerize, but the dimer can no longer add to the alkene to afford cyclobutanes **4** in anything but a very low yield because there is no alkene left.

Moreover, both **2** and **3** gave **4** in roughly the same yield (quite variable but up to 34%), suggesting that there could be an intermediate capable of rotation prior to reaction with a second equivalent of DMC to afford **4**. Although we do not have proof of stepwise and reversible formation of cyclopropanes **10**, possibly through zwitterions **11**, Scheme 7, such a process would accommodate some of the results.

Scheme 7



(E= CO_2Me)

2: (*E*-isomer)
3: (*Z*-isomer)

11

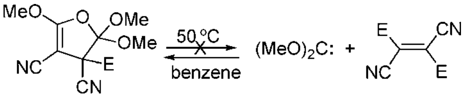
10

Zwitterions are well established intermediates in reactions of thiocarbonyl ylides with electrophilic alkenes, for example.[5,6] Reaction of **3** (more soluble in benzene than **2**) with the DMC precursor in benzene-d_6 at room temperature (3 weeks) also did not give any evidence (^{1}H NMR of the crude) of signals not attributable to **6**, *p*-methoxyacetophenone (a byproduct from the DMC precursor), and traces of **2**, **3** (**3** isomerizes to **2**), **4**, and **5**. We conclude that cyclopropane intermediates **10** are either not formed at all or are very reactive, reverting to **11**, which ultimately cyclizes to **6**.

1,4-Addition of DMC to **2** is sufficient to explain the formation of **6** and 1,4-addition of carbenes to conjugated systems is precedented,[7] although DMC itself gave such a product, after rearrangement, in only one case.[8]

In view of our reluctance to accept the formation of DMC dimer in the presence of alkene **2** we tried to find ways of getting to **4** from **6**. One way would be reversibility of the 1,4-addition process, to regenerate DMC and **2** from **6**, Scheme 8. Eventually DMC would dimerize and the dimer would add to **2** to generate **4**. A control experiment, in which **6** was heated in benzene for 24 h, left nearly all of the **6** intact, showing that **6** does not revert to DMC and **2** under the reaction conditions. A very small amount of **7** was the only impurity.

Scheme 8



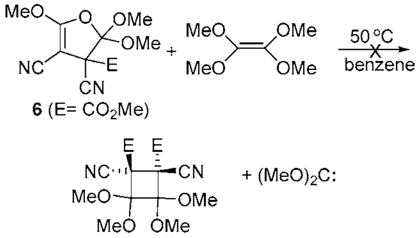
6 (E= CO_2Me)

DMC

2

Another potential source of **4** was investigated. Addition of DMC to **6** is relatively slow, because **6** could be isolated in the presence of **5**. Thus **6** and the carbene dimer could coexist if **2** is treated with >1 equiv of DMC. If **6** were then to react with the dimer to afford **4**, in competition with addition of DMC to **6** to afford **5**, one pathway to **4** would have been elucidated, Scheme 9. Although it looked unlikely, the reaction was attempted. Heating **6** with 1 equiv of separately prepared dimer did not afford any **4**, indicating that **6** does not afford **4** by that pathway either. We conclude that **6** does not give rise to **4** and that the latter probably originates from reaction of **2** with carbene dimer that was an unrecognized impurity in some samples of **1**. The origin of **4** is still under investigation.

Scheme 9



6 (E= CO_2Me)

4

In summary, the intermediacy of **6** in the formation of **5** and the unprecedented reaction of **2** to afford **7**, by sequential reaction with DMC and water, are reported. Compound **6** does not appear to lead to **4**.

Supporting Information Available: NMR spectra of **6** and **7** and an IR spectrum of **7**. This material is available free of charge via the Internet at http://pubs.acs.org.

OL071143U

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[7] (a) Winn, C. L.; Guillen, F.; Pytkowicz, J.; Roland, S.; Mangeney, P.; Alexakis, A. *J. Organomet. Chem.* **2005**, *690*, 5672. (b) Sugita, H.; Mizuno, K.; Mori, T.; Isagawa, K.; Otsuji, Y. *Angew. Chem.* **1991**, *103*, 1000. (c) Lambert, J. B.; Ziemnicka-Merchant, B. T. *J. Org. Chem.* **1990**, *55*, 3460.

[8] González, R.; Wudl, F.; Pole, D. L.; Sharma, P. K.; Warkentin, J. *J. Org. Chem.* **1996**, *61*, 5837.