HETEROCYCLES, Vol 28, No 1, 1989

PREPARATION AND DIELS-ALDER CYCLOADDITIONS OF SUBSTITUTED VINYLENE CARBONATES (1,3-DIOXOL-2-ONES) AND RELATED COMPOUNDS[1]

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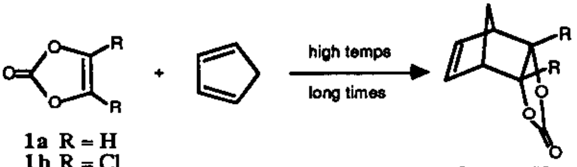
Abstract — Several substituted vinylene carbonates have been prepared by efficient routes and the dienophilicity of these and related compounds in Diels-Alder cycloadditions has been evaluated.

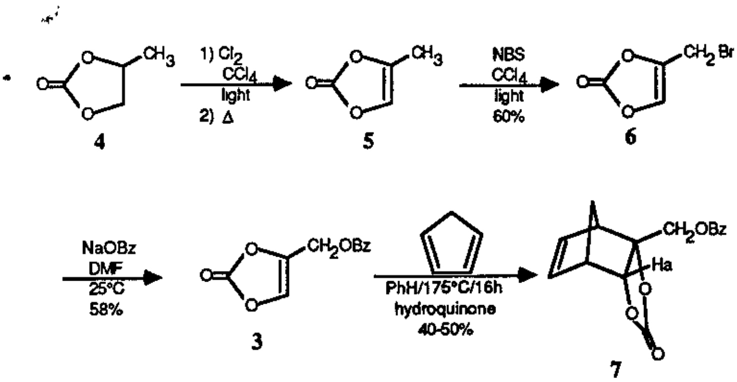
In the mid-1950's vinylene carbonate (1,3-dioxol-2-one) **1a** was first shown to act as a dienophile in Diels-Alder reactions with dienes.[3] Substituted derivatives of vinylene carbonates have rarely been used in cycloadditions, with the exception of the dichloro derivative (4,5-dichloro-1,3-dioxol-2-one) **1b**.[4] In most cases, however, high temperatures and long reaction times are required to achieve reasonable yields of the corresponding adducts **2ab** in these cycloadditions, even with reactive dienophiles such as cyclopentadiene. For the synthesis of several heavily oxygenated natural products, e.g., crotepoxide and showdomycin, we wanted to use substituted vinylene carbonates in Diels-Alder cycloadditions with reactive oxygenated dienes. Herein we describe the preparation of several substituted vinylene carbonates by efficient routes including some with electron-withdrawing groups, which allow cycloadditions with reactive dienes such as cyclopentadiene to be carried out at ambient temperature in high yields.



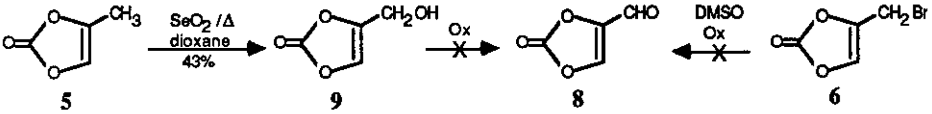
1a R = H
1b R = Cl

2a R = H
2b R = Cl

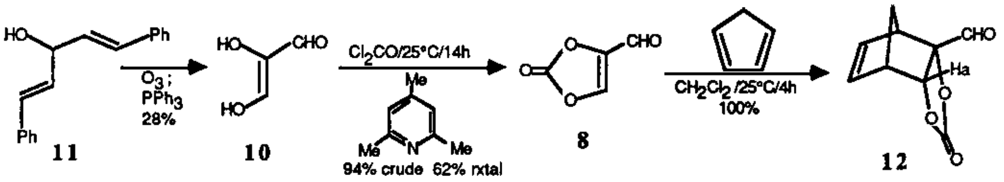
The first derivative we chose to prepare was 4-benzoyloxymethyl-1,3-dioxol-2-one, **3**. This was readily prepared from 4-methyl-1,3-dioxol-2-one **5** (itself prepared by chlorination-dechlorination of commercially available propylene carbonate **4** by the Newman and Addor[3a] method). Bromination of **5** with NBS in CCl_4 and sun lamp irradiation gave the known 4-bromomethyl compound **6** in 60% yield. Displacement of the bromide by sodium benzoate in DMF at 25°C afforded the desired benzoate **3** as a crystalline solid (mp 101-102°C) in 58% yield.[5] This compound was approximately as reactive as vinylene carbonate, giving the desired cycloadduct **7** in 40-50% yield upon heating a benzene solution of **3** with cyclopentadiene and a trace of hydroquinone at 170-175°C for 16h. The stereochemistry of **7** was assigned as shown with the carbonate endo by virtue of the ^{1}H nmr spectrum in which the proton α to the carbonate (Ha) appeared at 4.96 ppm as a doublet with $J=4$ Hz, indicating that the proton was exo. Thus the transition state with the carbonate endo is more stable as expected from the earlier cycloadditions with vinylene carbonate itself.



The second target was 2-oxo-1,3-dioxole-4-carboxaldehyde **8**, which, it was hoped, would be much more reactive in Diels-Alder cycloadditions than **1** or **3** due to the presence of the electron-withdrawing formyl group. The initial attempts to prepare **8** from the 4-methyl compound **5** by oxidation failed. For example the alcohol **9** (prepared from **5** by selenium dioxide oxidation in dioxane in 43% yield) could not be successfully oxidized to **8** by a variety of oxidation methods (PCC, Collins, MnO_2, chromic acid, etc.). Nor could the bromide **6** be oxidized to **8** by various DMSO-based oxidation routes. Therefore an alternate route for the preparation of **8** was investigated.

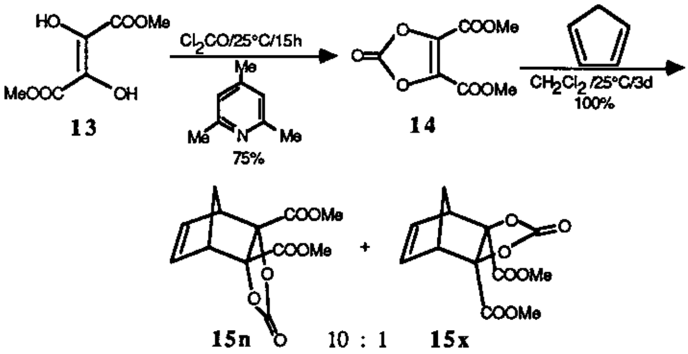


Hartmann was able to prepare substituted vinylene carbonates from symmetrical acyloins by reaction with phosgene and base.[6] To apply this route to **8**, we required a good route to the unsymmetrical acyloin, 2,3-dihydroxyacrolein (2-hydroxymalondialdehyde) **10**. This compound, also known as triose reductone, has been prepared by several routes. We were unable to prepare useful quantities by the lead tetraacetate oxidation of glucose[7] and thus turned to the ozonolysis of distyryl carbinol **11**.[8] We modified the known route somewhat by carrying out the ozonolysis in methylene chloride and destroying the ozonide with triphenylphosphine.[9] In this manner, **10** was obtained from **11** in 28% yield on a fairly large scale. Treatment of **10** with phosgene in the presence of 2,4,6-collidine afforded the desired formylvinylene carbonate **8** in 94% crude yield. Recrystallization from anhydrous ether gave in 62% yield the pure compound **8** [mp 76-7°C; ^{1}H nmr (acetone-d_6) δ 9.62 (1H, s), 8.53 (1H, s); ir (CH_2Cl_2) 1855 (s), 1705 (s), 1635 cm^{-1}]. With **8** in hand, we were able to test its dienophilicity in Diels-Alder reactions. Stirring a solution of **8** and cyclopentadiene in methylene chloride at 25°C for 4h resulted in the quantitative formation of a single product, namely the desired cycloadduct **12**. Again the stereochemistry of the adduct **12** was assigned as that shown, namely with the carbonate endo, due to the ^{1}H nmr spectrum, in which the proton α to the carbonate (Ha) appeared at 5.03 ppm as a doublet with J=4 Hz, indicating that the proton was exo. Thus the more stable transition state for the cycloaddition is that



in which the vinylene carbonate unit is endo while the formyl group is exo rather than the opposite arrangement. It should be noted that these are the mildest conditions for a successful cycloaddition with any vinylene carbonate reported to date, due no doubt to the small steric bulk and strong electron-withdrawing nature of the formyl substituent.

We also examined the possibility of preparing vinylene carbonates bearing two electron-withdrawing substituents. The known[10] dimethyl dihydroxyfumarate **13** (prepared by esterification of the commercially available dihydroxyfumaric acid with methanol and HCl) was treated with phosgene and 2,4,6-collidine to give the desired dimethyl 2-oxo-1,3-dioxole-4,5-dicarboxylate [bis(carbomethoxy)vinylene carbonate] **14** in 75% yield [mp 80-81°C; ^{1}H nmr ($CDCl_3$) δ 3.95; ir (CH_2Cl_2): 1840 (s), 1745 (s), 1655 cm^{-1}]. Diels-Alder cycloaddition of **14** with cyclopentadiene was significantly slower than the corresponding reaction of **8** and cyclopentadiene, eventually requiring 3 days at 25°C to go to completion. Two products **15nx** were isolated in a 10:1 ratio. We have assigned the structure **15n**, with the



carbonate group endo, to the major isomer, based on the stereochemistry of addition of cyclopentadiene to the formylvinylene carbonate **8**. We believe that the lower reactivity of the bis(carbomethoxy)vinylene carbonate **14** as compared to the formylvinylene carbonate **8** is due to the fact that the two carbomethoxy groups can not both be coplanar and overlapping with the vinylene carbonate due to steric interference with each other. Thus only the in-plane ester can exert an electron-withdrawing effect on the olefin via resonance while the out-of-plane ester should hinder the cycloaddition sterically. A similar argument has been used to explain the lower reactivity of maleates vs. fumarates. It should be pointed out, however, that the bis(carbomethoxy)vinylene carbonate **14** is still a rather reactive dienophile, since it requires only ambient temperature to react completely with cyclopentadiene (67% complete after 24h, 95% complete after 48h), and thus is more reactive than other simple vinylene carbonates.

We decided to try to overcome this steric interaction of the two cis ester groups by forming the corresponding anhydride, namely the novel oxocarbon furo[3,4-*d*]-1,3-dioxole-2,4,6-trione, **16**. Treatment of dihydroxyfumaric acid **17** with phosgene and 2,4,6-collidine afforded a mixture of the desired carbonate 2-oxo-1,3-dioxole-4,5-dicarboxylic acid **18** [ir (CH_2Cl_2): 1845 (s), 1740 (s), 1650 cm^{-1}] and 2,4,6-collidine hydrochloride **19** in moderate yield. This mixture could not be separated by any of several techniques (extraction, sublimation, fractional crystallization) and thus was used as a mixture in the next reaction. Refluxing a solution of **18** and **19** in thionyl chloride for 13.5h furnished a mixture which contained, by ir analysis, the desired oxocarbon **16** [ir (CH_2Cl_2): 1880 (s), 1800 (s), 1780 (w),

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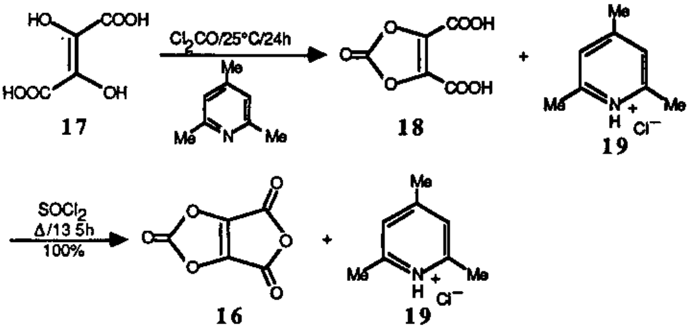
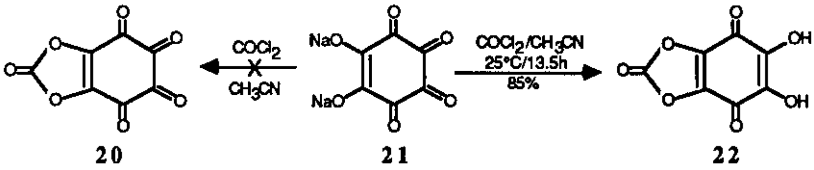
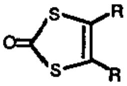
1650 cm^{-1}] along with collidine hydrochloride **19**. Again we were unable to separate **16** from the salt **19**, by any of several techniques. This inability to obtain the carbonate anhydride **16** in a pure state precluded the investigation of its reactivity towards dienes.



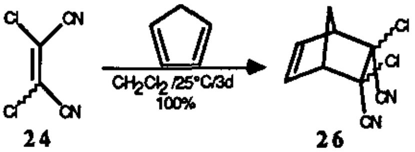
We tried to prepare one final vinylene carbonate substituted with two electron-withdrawing groups, namely the oxocarbon 1,3-dioxolo[4,5-*a*]cyclohexene-2,4,5,6,7-pentaone **20**. Treatment of the commercially available disodium salt of rhodizonic acid **21** with phosgene in acetonitrile at 25°C for 13.5h followed by non-aqueous workup and trituration with ether gave an 85% yield of the dihydroxyquinone carbonate **22** as a light yellow, extremely moisture-sensitive solid [ir (THF): 1940 (w), 1855 (s), 1730 (s), 1675 cm^{-1}; ^{13}C nmr (CD$_3$CN): δ 189.0, 144.0, 141.3, 140.7; ms (m/z) 198, 170, 142, 114, 86]. We have no good hypothesis for the source of the reducing agent which must be present in this reaction to account for the formation of **22** in preference to the desired oxocarbon **20**. We were unable to carry out any cycloadditions of **22** with dienes, possibly due to the acidity of the hydroxyl groups of **22** which may interfere with the desired reaction.



Finally we also tested the dienophilicity in Diels-Alder reactions with cyclopentadiene of two known highly substituted ethylenes, namely 2-oxo-1,3-dithiole-4,5-dicarbonitrile **23**[11] and 1,2-dichloro-1,2-dicyanoethylene **24** as a mixture of E and Z isomers.[12] The parent 1,3-dithiol-2-one **25** has been reported to be unreactive in normal Diels-Alder reactions under the same conditions that give high yields with vinylene carbonate. We hoped that substitution of **25** with the sterically small and strongly electron-withdrawing cyano groups might cause the molecule **23** to be reactive in cycloadditions. However reaction of **23** with cyclopentadiene at 25°C for two weeks gave back only starting material with no cycloadduct being formed. However the mixture of E and Z 1,2-dichloro-1,2-dicyanoethylene **24**, prepared in one step by chlorination of succinonitrile,[12] was quite reactive in Diels-Alder cycloadditions, giving a quantitative yield of the mixture of cycloadducts **26** after 3 days at 25°C.



23 R = CN
25 R = H



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In summary, we have prepared several new substituted vinylene carbonates and have tested their dienophilicity and that of related compounds in Diels-Alder reactions with cyclopentadiene.

ACKNOWLEDGEMENT

We thank the National Institutes of Health (CA-18164) for support of this research.

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Received, 5th August, 1988