Pergamon

Tetrahedron Letters, Vol. 37, No. 13, pp. 2149-2152, 1996

0040-4039/96 $15.00 + 0.00

S0040-4039(96)00235-3

Diels-Alder Reactivity of a Ketovinylphosphonate with Cyclopentadiene and Furan.

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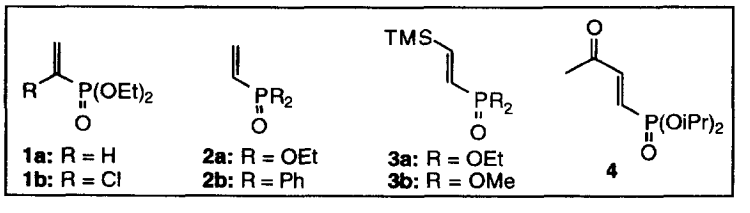
Summary: The Diels-Alder reactions between diethyl ketovinylphosphonate **5** and cyclopentadiene or furan were performed with and without Lewis acid assistance. The acetyl group directed endo in all cases, with ratios varying from 1.4:1 - 6.7:1 (acetyl endo).

Dialkyl ketovinylphosphonates have seen limited use as dienophiles in the Diels-Alder reaction, presumably due to the lack of ready availability of these compounds. Vinylphosphonates also exhibit lower Diels-Alder reactivities when compared to acrylate derivatives. Early reports by Daniewski and coworkers on the simple vinylphosphonates **1a,b** illustrated the lack of selectivity of these dienophiles under thermal conditions with various acyclic dienes.[3] Investigation by Buono and Maffei of the Diels-Alder reactions between **2a,b** and cyclopentadiene with and without Lewis acid assistance indicated that the Lewis acids increased the endo:exo ratio from about 1:1 (thermal) to approx. 3:1 - 5:1 (major = phosphonate endo). With the silyl group present (**3a,b**), the ratios were 1:1.5 (major = TMS endo) without Lewis acids, and up to 7.3:1 (major = phosphonate endo) with Lewis acids.[4]

Few reports are available, however, on the use of dialkyl ketovinylphosphonates as dienophiles in Diels-Alder reactions. Zbiral and coworkers found that the reaction of ketovinylphosphonate **4** with cyclopentadiene in refluxing chloroform gave a 3:1 ratio of endo:exo isomers with the acetyl group directing endo.[5] To our knowledge, there have been no studies on the effects of Lewis acids on the Diels-Alder reactivity of ketovinylphosphonates analogous to **4** or **5**. Since we wanted to use the Diels-Alder adduct between **5** and various dienes for our syntheses of phosphonate analogs of inositol phosphates[6], we felt that we first needed to clarify the reactivity of the diethyl ketovinylphosphonate **5** under various conditions with several dienes.



1a: R = H **1b:** R = Cl **2a:** R = OEt **2b:** R = Ph **3a:** R = OEt **3b:** R = OMe **4**

The ketovinylphosphonate (KVP) **5** was readily prepared on multigram scale using our pentacovalent oxaphospholene methodology.[7] The Diels-Alder system we initially investigated was the reaction of **5** and cyclopentadiene, with and without Lewis acid assistance. We initially found results similar to those of Zbiral, that is, the acetyl group directed under all the conditions we used forming the bicycles **6** and **7**. See **Table 1**. We could reproduce Zbiral's results without any Lewis acid and at 0 °C, instead of refluxing chloroform. Use of 1.2 equivalents of $ZnCl_2$ or $LiClO_4$ produced very similar product ratios relative to each other and to the non-

assisted reactions. The use of 2 or more equiv. of the Lewis acids, as well as lower reaction temperatures[8], helped to increase the endo:exo ratios. The lanthanide Lewis acid, $Eu(fod)_3$, has given the best ratios to date.

Scheme 1

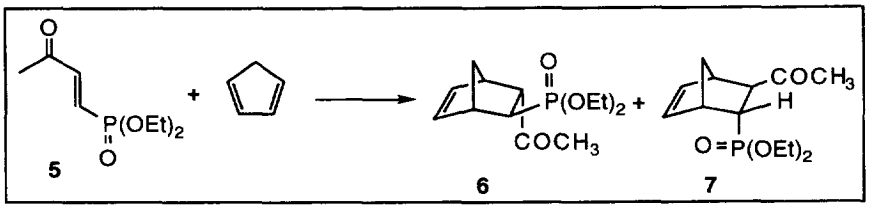


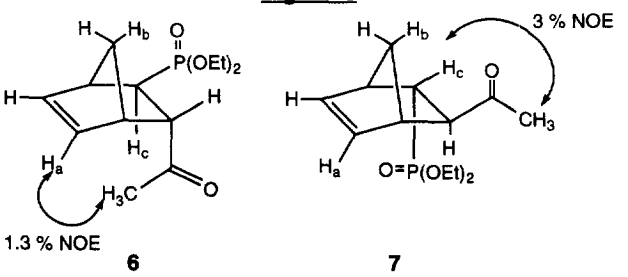
TABLE 1

Time	Temp	Lewis acid, equiv., solvent	6:7[a]	Yield[b]
1 hr	0° C	none, CH_2Cl_2	2.6 : 1.0	93
4 hrs	70° C[c]	none, $CHCl_3$	2.5 : 1.0	94
25 min	0° C	$ZnCl_2$, 1.2, CH_2Cl_2	3.3 : 1.0	94
20 min	0° C	$ZnCl_2$, 1.2, Et_2O	2.7 : 1.0	99
5 min	0° C	$ZnCl_2$, 25, Et_2O	4.5 : 1.0	92
20 min	0° C	$LiClO_4$, 1.2, CH_2Cl_2	2.5 : 1.0	95
25 min	0° C	$LiClO_4$, 1.2, Et_2O	2.4 : 1.0	99
5 min	0° C	$LiClO_4$, 25, Et_2O	3.6 : 1.0	97
10 min	0° C	$Eu(fod)_3$, 1.0, CH_2Cl_2	4.0 : 1.0	96*
15 hr	-40° C	$Eu(fod)_3$, 1.0, CH_2Cl_2	4.6 : 1.0	94*
3 min	0° C	$Eu(fod)_3$, 2.0, CH_2Cl_2	4.2 : 1.0	97*
50 min	-20° C	$Eu(fod)_3$, 2.0, CH_2Cl_2	6.7 : 1.0	96*

[a] ratio determined by ^1H-NMR integration.
[b] Yields reported are crude yields, except where noted by * which are isolated yields
[c] Zbiral's conditions with the diisopropyl phosphonate, **4**

Identification of the two diastereomers **6** and **7** was difficult due to overlapping resonances and ^1H-^{31}P coupling. Assignments proceeded by initially performing a 2D-COSY experiment to assign the chemical shifts. Nuclear Overhauser effect (NOE) experiments were then used to verify the identity of the acetyl endo isomer, **6.** The methyl group on the acetyl in **6** spends a fraction of its time during its free rotor movement near the vinyl proton, H_a (**Figure 1**). Irradiation of the CH_3 using a nuclear Overhauser sequence proved this to be the case as the NOE difference spectra of **6** exhibited an NOE of 1.3% for H_a. No enhanced signal for H_a was seen upon irradiation of the CH_3 in **7**. However, enhanced signals of 3.0 % for H_b and H_c were observed in **7**, thus proving that the acetyl was on the exo face. Proton-proton and carbon-phosphorus coupling constants corroborated our assignments.[9]

Figure 1



If complexation of 1 equiv. of Lewis acid was with the endo-directing acetyl oxygen, we should have seen better endo:exo ratios assuming that the secondary molecular orbital effects were predominating.[10] Calculation[11] of the Mulliken charges on the atoms in the phosphonic acid analog **8** clearly indicated the greater basicity of the phosphoryl oxygen O-6 over the carbonyl oxygen O-7 (**Table 2**). Experimental confirmation of this was obtained on **5** using ^{31}P, ^{13}C and ^{1}H NMR, as well as IR, spectroscopies. It was found via NMR that 1.0 eq. of $ZnCl_2$ coordinated with the phosphoryl oxygen in **5** as evidenced by the change in ^{31}P NMR chemical shift of the phosphorus, and the lack of any change in chemical shift of the carbonyl carbon in the ^{13}C NMR spectrum (**Table 3**). The IR spectrum of complexed **5** also indicated a large change in the P=O stretch and very little change in the C=O stretching frequency.[12]

Thus, the first equivalent of Lewis acid complexes with the phosphoryl oxygen and appears to have little effect on the LUMO energy or the molecular orbital coefficients of the MO's involved in the secondary orbital overlap, as evidenced by the small changes in endo:exo ratios with $ZnCl_2$ and $LiClO_4$. That fact that only 1 eq. of $Eu(fod)_3$ increased the endo/exo ratio more than the other Lewis acids may be due to an increased steric interaction. Complexation of $Eu(fod)_3$ to the phosphonate effectively increases the size of the phosphonate more than the other Lewis acids listed in **Table 1**, thus disfavoring the phosphonate endo product on steric grounds. A temperature effect was also seen with $Eu(fod)_3$ and is consistent with the increase of reagent selectivity generally seen with decreasing temperatures. *Ab initio* calculations are currently being performed on the phosphonic acid analog **8**, as well as its Lewis acid complexed species (mono- and di-complexed at P=O &/or C=O), in order to compare the molecular orbital coefficients and LUMO energy levels of each of these species. These calculations will be reported in due course.

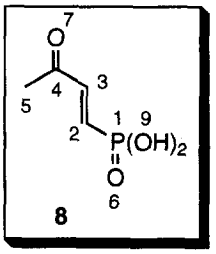


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Table 2

Atom	Mulliken Charge
C-2	-0.263
C-3	-0.133
C-4	0.273
O-6	-0.582
O-7	-0.364
O-9	-0.603
O-9	-0.610
P-1	1.24

Table 3

^{31}P:	Control	1 eq. $ZnCl_2$
P-1	15.9 ppm	17.7 ppm
^{13}C:		
C-2	129.5 ppm	125.2 ppm
C-3	143.4 ppm	146.1 ppm
C-4	196.7 ppm	196.3 ppm
^{1}H:		
H-2	6.91 ppm	7.09 ppm
H-3	6.72 ppm	6.69 ppm
IR:		
P=O	1260 cm^{-1}	1226 cm^{-1}
C=O	1688 cm^{-1}	1684 cm^{-1}

Use of our ketovinylphosphonate **5** in Lewis acid catalyzed Diels-Alder reactions with furan is being pursued to produce various inositol phosphonate derivatives.[5] To date, we have been able to form the Diels-Alder adducts **9** and **10**[13] from the KVP **5** and furan in good yields with varying selectivities depending on the Lewis acid and reaction conditions used (**Scheme 2** and **Table 4**). The Lewis acids Ti(Oi-Pr)$_4$ and Cl-Ti(Oi-Pr)$_3$ gave only low conversions (25%), while $AlCl_3$ and $TiCl_4$ reacted with the furan. Interestingly, use of 1 eq. of Et_2AlCl at -25 °C produced more phosphonate endo product than seen with 1 eq. of the other Lewis acids. This result is consistent with FMO theory since initial Lewis acid complexation is with the phosphonate. We are currently screening larger Lewis acids to further investigate these effects and improve our ratios with both furan and cyclopentadiene. Please note that the adducts **9** and **10** undergo a retro-Diels-Alder reaction

slowly at room temperature. Isolation of the isomers for analysis was done at 0 °C. We have been able to prevent the retro-Diels-Alder reaction by bis-hydroxylating the alkene (cat. OsO_4/NMO) in the crude mixture of **9** and **10**. Details of the conversion of **9** to an inositol phosphonate derivative will be reported in due course.

Scheme 2

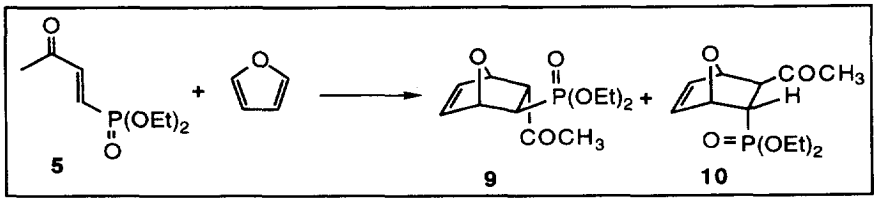

Table 4

Lewis acid (eq.)	Solvent / Furan	Temp. °C	**9** : **10**[a]	% Yield
$ZnCl_2$ (1.0)	1:1 CH_2Cl_2:furan	0	3.2 : 1.0	76
$ZnCl_2$ (25)	Et_2O/10 eq. furan	0	4.0 : 1.0	b
Et_2AlCl (1.0)	furan	0	3.6 : 1.0	70
Et_2AlCl (1.0)	furan	-25	1.4 : 1.0	86
Eu(fod)$_3$ (2.0)	CH_2Cl_2/10 eq. furan	0	4.0 : 1.0	b

[a] ratio determined by ^{1}H-NMR integration.

[b] products not purified (crude yield approx. quantitative), but taken on to diol (*vide supra*)

Acknowledgments: This work was funded in part by the University of Delaware Honors Undergraduate program (KBH), a University Exploratory Research Program Award from Procter and Gamble (CKM), and by the Donors of The Petroleum Research Fund administered by the American Chemical Society.

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(*Received in USA* 6 *December* 1995; *revised* 24 *January* 1996; *accepted* 30 *January* 1996)