Tetrahedron Letters, Vol. 34, No. 29, pp. 4587-4590, 1993
Printed in Great Britain

0040-4039/93 $6.00 + .00
Pergamon Press Ltd

Synthesis and Reactions of Achiral 3-Substituted Vinylketene Acetals as Dienes in the Diels-Alder Reaction

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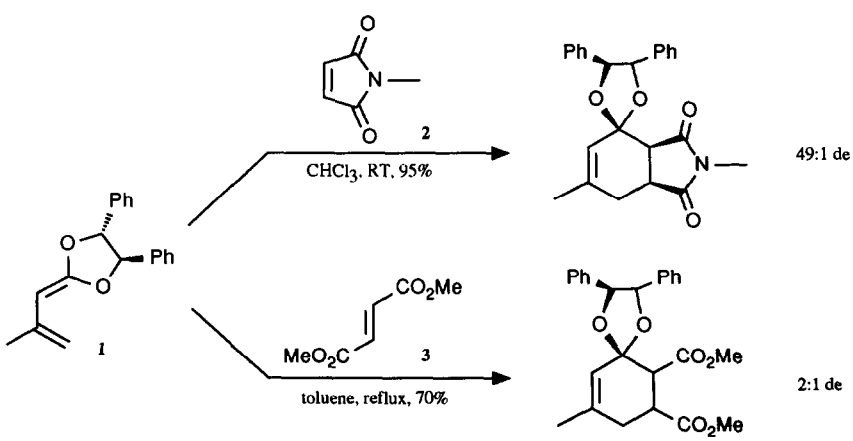
Abstract: The synthesis of three new vinylketene acetals, each bearing a heteroatom substituent at C3 of the diene unit, and their reactions with representative dienophiles in Diels-Alder reactions are presented. All the dienes react well at room temperature, indicating substantial activation of the cycloaddition event. The stereochemistry of the major Diels-Alder product of a 3-SPh-substituted vinylketene acetal is opposite to that produced by the corresponding 3-unsubstituted compound.

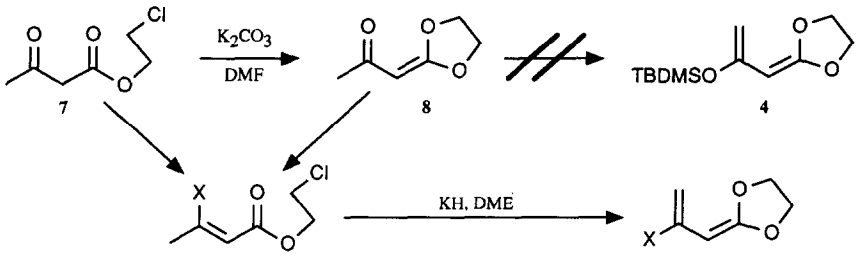
Pioneering work by Danishefsky, Brassard, and others[2] on the use of highly substituted dienes in the Diels-Alder reaction expanded this extremely versatile approach to the synthesis of multi-functionalized 6-membered rings. The recent literature attests to the continued vitality of this methodology.

A program on the chemistry of enantiomerically pure ketene acetals was initiated recently in which the focus was on the Diels-Alder reactions of vinylketene acetals[3] and the reactions of acylketene acetals with polar reagents.[4] The electron-rich, enantiomerically pure ketene acetal activates the diene toward cycloadditions while functioning as both a chiral auxiliary for the reaction and a protecting group for the enone functionality generated in the event. Indeed, a high degree of selectivity was documented with diene **1** and *N*-methylmaleimide (**2**), as shown below. However, the reactivity and selectivity of **1** is not adequate when less reactive dienophiles such as diethyl fumarate (**3**) are employed.



Certain total synthesis projects under consideration in this laboratory would require the use of vinylketene acetals in cycloaddition reactions with dienophiles other than *N*-methylmaleimide. Herein the results on the synthesis and reactivity of three achiral vinylketene acetals (**4-6**), each of which is substituted at C3 of the diene unit with a heteroatom, are presented. These 1,1,3-trisubstituted and 1,1,3,4-tetrasubstituted (*vide infra*) dienes are highly functionalized, easily prepared compounds which demonstrate excellent reactivity in cycloaddition reactions.

Initially, the synthesis of 3-substituted dienes **4-6** was envisioned as originating from the corresponding β-keto ester **7** via acylketene acetals **8** employing methodology which had been explored in the course of previous studies.[4] However, as shown below, attempts to convert acylketene acetal **8** to the corresponding *t*-butyldimethylsilyloxy diene by any combination of reaction conditions met with failure. Instead, corresponding β-chloroethyl ester **9**[5] was routinely obtained. Dienes **4-6** were prepared by initial formation of desired β-substituted esters **9-11** (TBDMSCl/NEt_3; morpholine/benzene/4Å sieves; $PhSH/P_2O_5$,[6,7] yields given below), followed by our standard vinylketene acetal synthesis protocol. In this way, good yields of the desired diene could be routinely obtained.

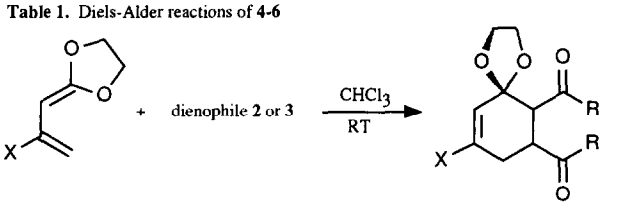


9 X = OTBDMS, 82% from both **7** and **8**
10 X = morpholino, 71% from **8**
11 X = SPh, 55% from **8**

4 X = OTBDMS, 79%
5 X = morpholino, 65%
6 X = SPh, 88%

The results of the initial [4+2] reactions with **4-6** are shown below in Table 1. The dienes are quite reactive toward **2**, as expected. In addition, the reactivity toward dimethyl fumarate is exceptional, again producing only one compound in excellent yield at room temperature. All reactions afford a single compound by 250 MHz NMR.

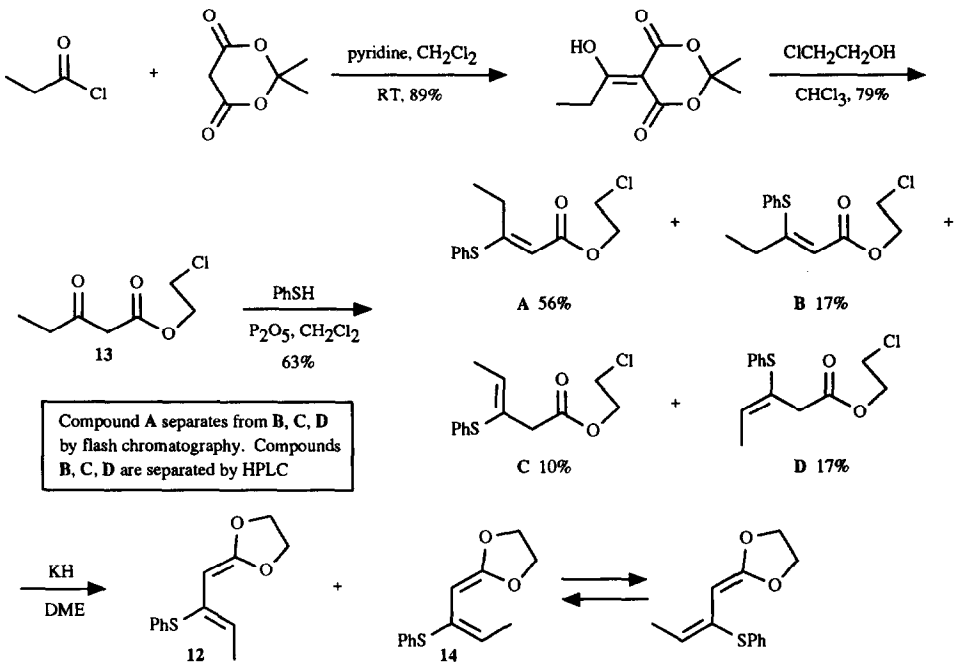
Table 1. Diels-Alder reactions of **4-6**



Entry	Diene	Dienophile	Time	% Yield[a,b]
1	**4**, X = OTBDMS	**2**	8 h	93
2	**4**, X = OTBDMS	**3**	48 h	93
3	**5**, X = NC_4H_8O	**2**	12 h	86
4	**5**, X = NC_4H_8O	**3**	96 h	80
5	**6**, X = SPh	**2**	8 h	>95 (49[c])
6	**6**, X = SPh	**3**	74 h	>95 (68[c])

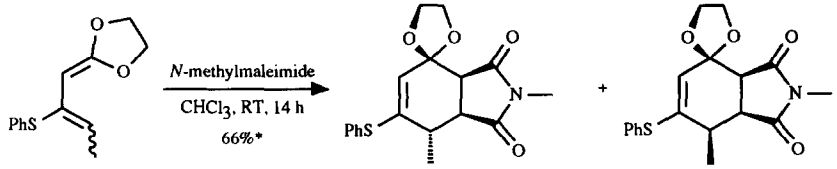
a) High-field NMR of product indicates one new compound consistent with the assigned structure. b) direct mass yield. c) yield after chromatography.

The 3-SPh substituent allows for the products to be isolated by conventional methodology. In addition, the synthetic utility of vinyl sulfides is well established.[6,8] Therefore, dienes with structure **6** were chosen for further experimentation. In the earlier work from this laboratory,[3b] *exo* stereochemistry in the Diels-Alder reactions of **1** had been observed. To probe this aspect of the Diels-Alder reaction with the present systems, diene **12** was prepared by the method shown below. The requisite β-ketoester **13** was prepared via the standard Meldrum's acid procedure[9] and subjected to $PhSH/P_2O_5$ treatment. A mixture of all four possible stereoisomers was formed in the indicated ratio, which led to a 60:40 mixture of dienes **12** and **14**.



The origin of this mixture of **12** and **14** was probed by isolating pure stereoisomers **A** and **C** and subjecting them to diene formation conditions. In each case, the same 60:40 mixture of **12** and **14** were obtained. Thus, allyl anion formation and loss of stereochemical integrity precede ketene acetal formation. Stereospecific formation of desired *Z*-olefins of type **12** must therefore be approached through variations in conditions within the current reaction manifold or alternative routes to vinylketene acetals must be developed.

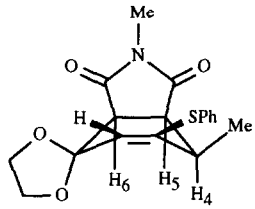
Isomer **14** is expected to be unreactive due to the predominance of the s-trans conformation, as depicted above. In the event, only diene **12** reacted with *N*-methylmaleimide. Gratifyingly, the reaction proceeds to completion in 14 h at room temperature with this 1,1,3,4-tetrasubstituted diene. Analysis by high field NMR, including NOE measurements as shown below, indicates that the major isomer arises from the *endo* approach of the maleimide to the diene.[10] This is opposite to the reaction of the corresponding compound without the



* Yield based on reacting *Z* isomer. *E* isomer is totally unreactive under these conditions.

-SPh group at C3.[3b] The origin of this change in stereochemistry is currently under study.

In conclusion, highly substituted vinylketene acetals of type **4-6** are highly reactive dienes in the Diels-Alder reaction that do not require Lewis acid activation to afford good yields of cycloaddition products under mild reaction conditions.[11]



Observed *J* values	Observed nOe
$J_{4,5}$ = 7.2 Hz	H_4 - H_5
$J_{5,6}$ = 10.5 Hz	H_5 - H_6
	H_4 - H_6

Notes and References

† Dedicated to Dr. N.R.Ayyangar on the occation of his 60th birthday.

1. Portions of this work were presented at the 204th Meeting of the American Chemical Society, Washington, DC, abstract ORGN 175.
2. a) Danishefsky, S. *Acc. Chem. Res.* **1981**, *14*, 400 and references therein. b) Banville, J.; Brassard, P. *J. Org. Chem.* **1976**, *41*, 3018. c) Grandmaision, J.-L.; Brassard, P. *J. Org. Chem.* **1978**, *43*, 1435. d) Grandmaision, J.-L.; Brassard, P. *Tetrahedron* **1977**, *33*, 2047. e) Savard, J.; Brassard, P. *Tetahedron Lett.* **1979**, *20*, 4911. f) Ley, S. V.; Mitchell, W. L.; Radhakrishnan, T. V.; Barton, D. H. R. *J. Chem. Soc., Perkin Trans. 1* **1981**, 1582.
3. a) Konopelski, J.P.; Boehler, M.A. *J. Am. Chem. Soc.* **1989**, *111*, 4515-7. Boehler, M.A.; Konopelski, J.P. *Tetrahedron*, **1991**, *47*, 4519-38.
4. Eid, Jr., C.N.; Konopelski, J.P. *Tetrahedron*, **1991**, *47*, 975-92, and references therein.
5. The same single isomer is obtained from both **7** and **8**; we have shown it as the *Z*-isomer in accord with previous observations on acylketene acetal chemistry.
6. Trost, B.M.; Lavoie, A.C. *J. Am. Chem. Soc.* **1983**, *105*, 5975-90.
7. Subsequent to this work it was discovered that 75%-85% yields of 3-SPh diene precursors could be routinely obtained with PhSH and catalytic *p*-toluenesolfonic acid in refluxing toluene with azeotropic removal of water.
8. See, for example, Tamao, K. Coupling Reactions Between sp^3 and sp^2 Carbon Centers. In *Comprehensive Organic Synthesis*; Trost, B.M., Ed.; Pergammon: 1991; Vol 3., pp. 446.
9. Oikawa, Y.; Yoshioka, K.; Sugano, K. Yonemitsu, O. *Org. Synth.* **1984**, *63*, 198-202, and references therein.
10. Major isomer data: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.26 (d, *J* = 7.2 Hz, 3H), 2.86 (p, *J* = 7.2 Hz, 1H), 2.99 (s, 3H), 3.24 (dd, *J* = 10.5, 7.2 Hz, 1H), 3.35 (d, *J* = 10.5 Hz, 1H), 3,86 (m, 2H), 4.01 (m, 1H), 4.24 (m, 1H), 5.43 (s, 1H), 7.35-7.44 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 16.44, 24.80, 33.18, 43.35, 49.17, 65.11, 66.24, 104.48, 125.08, 128.83, 129.53, 130.87, 133.89, 146.76, 174.51, 176.98; IR (neat) 1718, 1710 cm^{-1}; MS (EI) *m/z* 345 (M^+, 10%), 125 (100%).

11. This research was supported by funds provided by the Cigarette and Tobacco Surtax Fund of the State of California through the Tobacco-Related Disease Research Program of the University of California, Grant Number 2RT0004.

(Received in USA 10 May 1993)