Tetrahedron Letters,Vol.26,No.11,pp 1395-1398,1985
Printed in Great Britain

0040-4039/85 $3.00 + .00
©1985 Pergamon Press Ltd.

THE EFFECT OF SULFUR AND SELENIUM SUBSTITUTENTS ON THE REGIOCHEMISTRY OF DIELS-ALDER REACTIONS

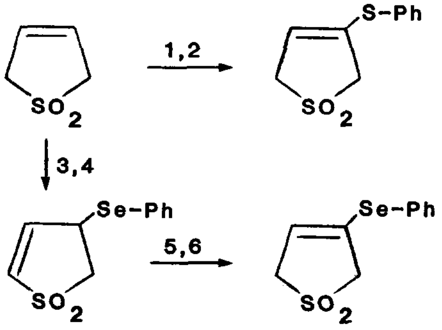
Charles L. Liotta*, and John W. Verbicky, Jr.
School of Chemistry, Georgia Institute of Technology, Atlanta, Georgia 30332 USA

SUMMARY: 2-Phenylthio-1,3-butadiene (1) and 2-phenylseleno-1,3-butadiene (2) have been generated *in situ* from their SO$_2$ adducts and reacted with a series of unsymmetrical dienophiles. The regiochemical results have been analyzed in terms of qualitative perturbation theory.

Whereas the Diels-Alder reaction provides a facile means of constructing six-membered rings[1], its greatest synthetic potential lies in the regioselectivity accompanying the cycloaddition of unsymmetrically substituted dienes and dienophiles. In particular, the use of unsymmetrical functionally masked reaction partners provides useful entries into multistep syntheses of complex molecules.

The understanding of the regiochemistry accompanying cycloaddition reactions has been approached experimentally as well as theoretically.[2-8] A wide variety of 1,3-butadienes substituted at the 1- or 2-positions have been reported. Most of these studies, however, have been concerned with first row substituents - carbon, nitrogen and oxygen. In contrast, very few regiochemical results have been published concerning corresponding second and third row substituents.[6,9-12] As a consequence, 2-phenylthio-1,3-butadiene (1) and 2-phenylseleno-1,3-butadiene (2) were chosen as synthetically and theoretically useful models. Because of the tendency of these dienes to undergo facile polymerization reactions upon purification or storage, they were generated *in situ* from their SO$_2$ adducts in the presence of the dieneophile.[11,13] The syntheses of the SO$_2$ adducts are outlined in Scheme I. The yields, regiochemical results and relative rates of reaction with a variety of dienophiles are summarized in Table I. Control experiments indicate that the results are independent of the

Scheme I



Reagents: 1. Ph-SH, NCS, CH$_2$Cl$_2$, r.t., 24 hrs.; 2. (C$_2$H$_5$)$_3$N, CH$_2$Cl$_2$, r.t., 24 hrs.; 3. Ph-Se-Cl, CH$_2$Cl$_2$, Argon, r.t., 24 hrs.; 4. (C$_2$H$_5$)$_3$N, r.t., 24 hrs.; 5. DBU, HCCl$_3$, -23°, 1 hr.; 6. HCl, NaHCO$_3$.

presence of SO_2. The isolated yields of cycloaddition products are consistently excellent for both 1 (90-97%) and 2 (80-95%). In general, 1 reacts almost twice as fast as 2 with a given dienophile. In addition, the regiochemical results indicate that the sulfur substituent has a strong directive effect and is somewhat better than the corresponding selenium substituent.

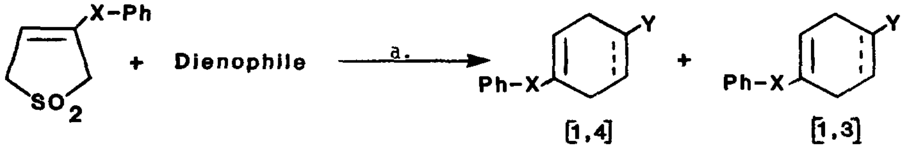
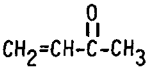
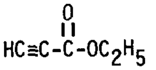
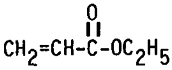


TABLE 1

Dienophile	$t_{1/2}$ (hrs.)		Isolated Yield (%)		[1,4] (%)		[1,3] (%)	
	S	Se	S	Se	S	Se	S	Se
 $CH_2{=}CH{-}\overset{\overset{O}{\|}}{C}{-}CH_3$	2.9	5.25	97	96	91	82	9	18
 $HC{\equiv}C{-}\overset{\overset{O}{\|}}{C}{-}OC_2H_5$	5.0	7.6	93	79	83	72	17	28
 $CH_2{=}CH{-}\overset{\overset{O}{\|}}{C}{-}OC_2H_5$	5.0	7.5	95	94	91	80	9	20
$CH_2{=}CH{-}CN$	6.7	13.25	90	81	>95	>95	<5	<5

a. 110°C, dry toluene, dark, Argon atm., 1% hydroquinone.

The regiochemical results in Table I are consistent with frontier molecular orbital theory. It is instructive to visualize this without performing detailed computer calculations. The polarization of the highest occupied molecular orbital of the 2-substituted diene may be qualitatively determined from perturbation theory by evaluating the orbital mixings obtained from the interaction of the electron-pair on the heterosubstituent with the 2-position of the butadiene π-system. Consider, for example, the analysis of the highest occupied molecular orbital of 2-phenylthio-1,3-butadiene (1). The π-system of this molecule may be disected into two fragments, one consisting of the π-system of 1,3-butadiene and the other a pair of electrons in a p-orbital of sulfur conjugated to a phenyl ring. At an infinite separation there is no interaction between the two fragments. However, as they are brought together and joined at the 2-position of 1,3-butadiene, the orbitals of each perturb one another and produce diene π-polarization. In order to analyze this system using perturbation theory, the molecular orbital wave functions (nodal properties) for each fragment must be known as well as their relative energy levels. The energy levels for the fragments comprising 1 are illustrated in Figure 1.[14] The highest occupied molecular orbital of the the two fragments is ψ_{PhS}, and therefore, it is the sum of the first-order mixings of ψ_{PhS} with each of the molecular orbitals of the diene system (ψ_1, ψ_2, ψ_3 and ψ_4) (not equally weighted) which primarily determines the net polarization of the diene π-HOMO.[15] The qualitative individual first-order mixings are illustrated in Figure 2. If one considers only the polarization of the diene portion of the molecule, it is obvious that this sum of first order interactions (not equally weighted) places the largest HOMO coefficient at the terminal position closest to the sulfur substituent. Thus, this position is the leading center in bonding with the dienophile center having the coefficient of greatest magnitude in the LUMO. This analysis is consistent with the predominance of the 1,4-products in the reported Diels-Alder reactions. The energy of the lone pair on selenium in the phenylseleno substituent is at -8.0 ev and the qualitative perturbational analysis for 2 is identical to that of the sulfur counterpart.[16]

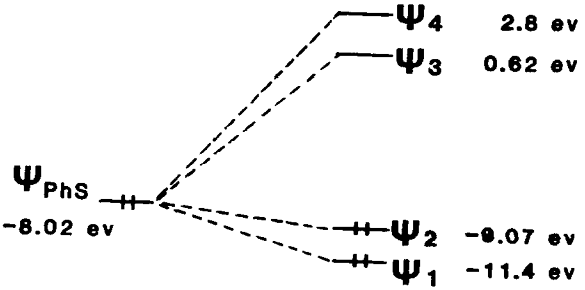


Figure 1

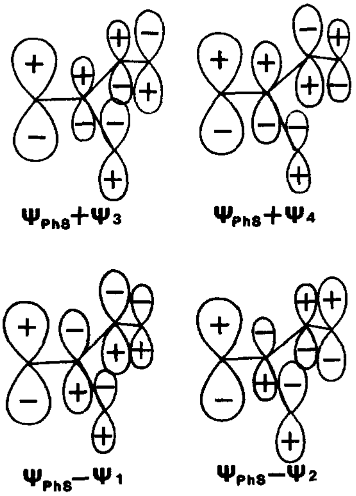


Figure 2

Since the electron pairs on sulfur and selenium are at essentially the same energy, the greater directive effect and the greater reactivity of PhS- compared to PhSe- must arise in part from the larger resonance integral describing the interaction of a 3p-π orbital on sulfur with a 2p-π orbital on carbon as compared to a 4p-π orbital on selenium with a 2p-π on carbon.[17] The larger the resonance integral, the greater the π-polarization of the diene portion of the molecule and the less negative the HOMO energy. The former results in a greater differentiation between the coefficients on the terminal atoms of the diene (greater regioselectivity) while the latter results in a smaller frontier energy gap with respect to the LUMO of a given dienophile (greater reactivity).

In conclusion, the combination of high isolated yields and excellent regiochemical control makes 1 and 2 excellent masked carbonyl Diels-Alder reaction partners. In addition, the use of latent dienes, in the form of crystalline, easily prepared and stable SO_2 adducts make both 1 and 2 potentially useful reagents in synthesis. Finally, the regiochemical results are entirely consistent with qualitative perturbational analysis and frontier molecular orbital theory.

REFERENCES:

1. O. Diels and K. Alder, *Ann.*, *98*, 460 (1928).
2. J. Sauer, *Angew. Chem. Int. Ed. Engl.*, *6*, 16 (1967).
3. I. Fleming, *Frontier Orbitals and Organic Chemical Reactions*, Wiley-Interscience; John Wiley & Sons, New York, NY, p. 121-140 (1976).
4. K. N. Houk, *Acc. Chem. Res.*, *8*, 361 (1975), and references cited therein.
5. O. Eisenstein, J. M. Lefour, N. T. Anh and R. F. Hudson, *Tetrahedron*, *33*, 523 (1977), and references cited therein.
6. P. V. Alston *et al.*, *J. Org. Chem.*, *48*, 5051 (1983) and references cited therein.
7. W. C. Herndon, *Chem. Rev.*, *72*, 157 (1972).
8. N. D. Epiotes, *J. Am. Chem. Soc.*, *95*, 5624 (1973).
9. D. A. Evans, C. A. Bryan and C. L. Sims, *J. Amer. Chem. Soc.*, *94*, 2891 (1972).
10. A. J. Bridges and J. W. Fischer, *J. Org. Chem.*, *49*, 2954 (1984).
11. P. B. Hopkins and P. L. Fuchs, *J. Org. Chem.*, *43*, 1208 (1978) and references cited therein.
12. B. M. Trost *et al.*, *J. Amer. Chem. Soc.*, *102*, 3554 (1980) and references cited therein.
13. L.F. Hatch and T.E. Sample, *Org. Syn.*, *50*, 43 (1970).
14. The energy of the electron pair primarily localized in the 3p orbital of a sulfur conjugated with a phenyl ring and the energies of the occupied π-molecular orbitals (ψ_1 and ψ_2) of 1,3-butadiene have been determined by means of photoelectron spectroscopy: A. Schweig and N. Thon, *Chem. Phys. Letters*, *38*, 482 (1976); M. J. S. Dewar and S. D. Worley, *J. Chem. Phys. 49*, 2454 (1968). The energies of the unoccupied π-molecular orbitals (ψ_3 and ψ_4) of 1,3-butadiene have determined from electron transmission spectroscopy: P. D. Burrow and K. D. Jordan, *Chem. Phys. Lett.*, *36*, 594 (1975).
15. The first order mixing coefficient c_j describing the mixing of ψ_i with ψ_j is $c_j = H_{ij}/(E_i - E_j)$ where H_{ij} is the resonance integral (a negative number) and E_i and E_j are the energies of ψ_i and ψ_j, respectfully, expressed in ev's. Thus, the final unnormalized wave function describing the HOMO of *1* is $\psi_{HOMO} = \psi_{PhS} + c_1\,\psi_1 + c_2\,\psi_2 + c_3\,\psi_3 + c_4\,\psi_4$, where $C_1 = H_{\psi PhS\psi 1}/(E_{\psi PhS} - E_{\psi 1})$, $C_2 = H_{\psi PhS\psi 2}/(E_{\psi PhS} - E_{\psi 2})$, $C_3 = H_{\psi PhS\psi 3}/(E_{\psi PhS} - E_{\psi 3})$, $C_4 = H_{\psi PhS\psi 4}/(E_{\psi PhS} - E_{\psi 4})$; L. Libit and R. Hoffmann, *J. Am. Chem. Soc.*, *96*, 1370 (1974).
16. A. D. Baker, G. H. Armen, Y. Guang-di, D. Liotta, N. Flannagan, and C. Barnum, *J. Org. Chem.*, *46*, 4127 (1981).
17. The overlap integrals for C-C (1.52Å), C-S (1.82Å), and C-Se (1.95Å) are calculated to be 0.211, 0.159, and 0.148, respectively. The relative values of the resonance integrals are assumed to be the same relative order as the overlap integrals since inclusion of the usual Helmholz-Wolfsberg factors does not change this order; E. Clementi and D.L. Raimondi, *J. Chem. Phys.*, *38*, 2686 (1963) and E. Clementi, D.L. Raimondi, and W.P. Reinhardt, *J. Chem. Phys.*, *47*, 1300 (1967).

(Received in USA 19 November 1984)