

## DIELS-ALDER REACTIONS OF 2H-THIOPYRANS

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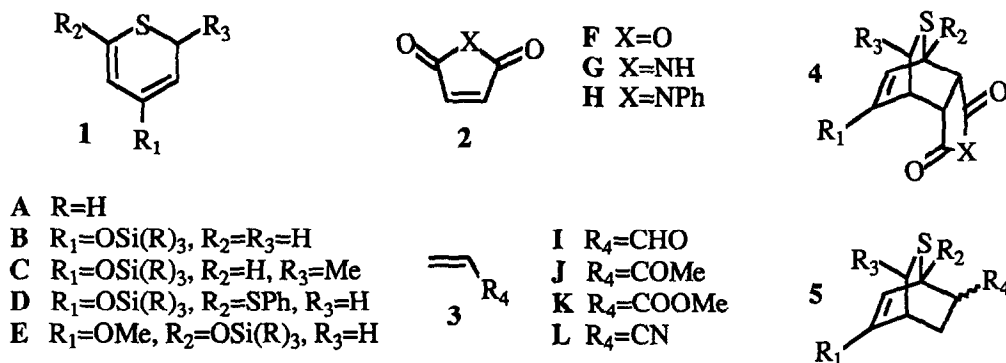
**Abstract:** Oxygenated 2H-thiopyrans react with typical dienophiles to produce predominantly endo adducts in modest to high yield. The adducts can be desulfurized to give compounds equivalent to a Diels-Alder adduct of a *cis*-diene.

The Diels-Alder reaction is of fundamental importance in synthetic organic chemistry<sup>1</sup>. A major limitation of this process is the lack of reactivity associated with dienes in which one (or both) of the double bonds is *cis*. The poor reactivity of *cis*-dienes is attributed to the steric crowding which occurs in the necessary *s-cis* conformation. In an effort to overcome this difficulty, we envisioned utilizing 2H-thiopyrans as functional equivalents to *cis*-dienes. In 2H-thiopyrans the required *s-cis* geometry is maintained by the cyclic structure. Reaction with dienophiles should provide adducts which, after desulfurization, are equivalent to those which would be produced from a *cis*-diene. In this way the scope of the Diels-Alder reaction could be significantly expanded.

The Diels-Alder reactions of 2H-thiopyrans have not been extensively studied. A single paper<sup>2</sup> reports that the parent compound (**1A**) reacts with typical dienophiles at high temperatures to give adducts in low yield. Whether the low yields obtained were due to the thermal instability of the adducts<sup>3</sup> or poor reactivity of the thiopyran was not determined. However, if this reaction is to be synthetically useful, the reactivity must be enhanced. The presence of electron donating substituents on the diene can dramatically increase Diels-Alder reactivity<sup>4</sup>. We have examined the Diels-Alder reactivity of several appropriately substituted 2H-thiopyrans<sup>5-7</sup>. The results are presented in Table 1.

The dienes **1B** and **1C** react with activated dienophiles **2** to provide the endo<sup>8</sup> adducts **4** in good yield. In the case of **1B**, the use of BHT was necessary to inhibit the formation of thiopyrone **6**. The presence of the methyl substituent in **1C** results in good diastereotopic face selectivity. The TMS (ie. R=Me) dienes **1B** and **1C** show a high propensity to revert to the corresponding enones despite attempts to rigorously exclude moisture. Thus a solution of **1B** (R=Me) in dry toluene(d<sub>8</sub>) is completely converted into the corresponding enone within 16h at 80°C (NMR). The use of TBDMS- (R=Me, Me, t-Bu) or especially TIPS- (R=iPr) dienes largely circumvents this reaction. Judging from the reaction time and/or temperature, the dienes **1D** and **1E** are more reactive than **1B**. The lower

yields obtained with these compounds is attributable to the instability of both the dienes and the adducts under the reaction conditions.

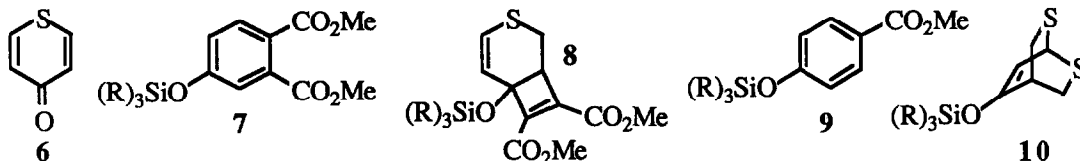


**Table 1.** Diels-Alder Reactions of 2H-Thiopyrans<sup>a</sup>

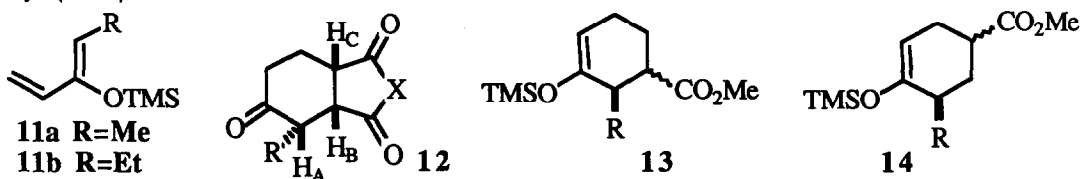
entry	diene	dienophile	temp(°C)	time(h)	product	yield(%)	endo:exo
1.	<b>1B</b> ( $\text{R}=\text{Me}$ ) <sup>b</sup>	<b>2G</b>	110 <sup>c</sup>	16	<b>4BG</b>	87 <sup>f,g</sup>	92:8
2.		<b>2H</b>	110 <sup>c</sup>	16	<b>4BH</b>	86 <sup>f,g</sup>	92:8
3.	<b>1B</b> ( $\text{R}=\text{Me,Me}$ $\text{tBu}$ ) <sup>b</sup>	<b>2F</b>	110 <sup>c</sup>	16	<b>4BF</b>	85 <sup>f,h</sup>	75:25
4.		<b>2G</b>	110 <sup>c</sup>	24	<b>4BG</b>	74 <sup>f</sup>	93:7
5.		<b>2H</b>	110 <sup>c</sup>	16	<b>4BH</b>	83 <sup>f</sup>	92:8
6.	<b>1B</b> ( $\text{R}=\text{iPr}$ )	<b>2F</b>	120 <sup>c</sup>	36	<b>4BF</b>	90 <sup>h</sup>	80:20
7.		<b>2G</b>	120 <sup>c</sup>	72	<b>4BG</b>	72	93:7
8.		<b>2H</b>	120 <sup>c</sup>	48	<b>4BH</b>	77	94:6
9.		<b>3I</b>	120 <sup>d,e</sup>	72	<b>5BI</b>	46	77:23
10.		<b>3J</b>	120 <sup>d,e</sup>	168	<b>5BJ</b>	41	70:30
11.		<b>3K</b>	120 <sup>d,e</sup>	144	<b>5BK</b>	56	62:38
12.		<b>3L</b>	120 <sup>d,e</sup>	144	<b>5BL</b>	43	50:50
13.	<b>1C</b> ( $\text{R}=\text{iPr}$ )	<b>2F</b>	110 <sup>d</sup>	36	<b>4CF</b>	90 <sup>h</sup>	81:19
14.		<b>2G</b>	110 <sup>d</sup>	36	<b>4CG</b>	81	90 <sup>k</sup> :10
15.		<b>2H</b>	110 <sup>d</sup>	36	<b>4CH</b>	75	88 <sup>k</sup> :12
16.		<b>3K</b>	150 <sup>d,e</sup>	250	<b>5CK</b>	60 <sup>f</sup>	55:45
17.	<b>1D</b> ( $\text{R}=\text{iPr}$ )	<b>2G</b>	110 <sup>c</sup>	16	<b>4DG</b>	43 <sup>f</sup>	75:25
18.		<b>2H</b>	110 <sup>c</sup>	16	<b>4DH</b>	59 <sup>f</sup>	80:20
19.	<b>1E</b> ( $\text{R}=\text{iPr}$ )	<b>2H</b>	80	4	<b>4EH</b>	40 <sup>f</sup>	81:19

(a) reactions conducted with 2eq. of dienophile. (b) 0.1 eq. of BHT was added. (c) in xylene. (d) in toluene. (e) sealed tube. (f) yield based on recovered hydrolyzed diene. (g) product isolated as the corresponding ketone. (h) yield based on NMR using an internal standard. (i) includes 6% of the Me epimer. (k) includes ca. 3% of the Me epimer.

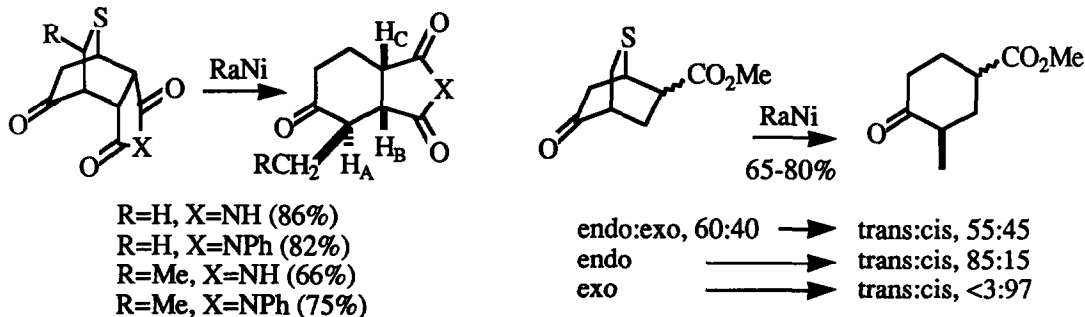
Diels-Alder adducts were not obtained with acetylenic dienophiles. For example reaction of **1B** (R=Me) with dimethyl acetylenedicarboxylate (conditions) gave a complex mixture of products of which **7** and **8** (R=Me) could be isolated in low yield. Similarly, reaction of **1B** (R=iPr) with methyl propiolate gave **9** and **10** (R=iPr) along with several unidentified products. The production of **7** and **9** is presumably the result of a facile retro Diels-Alder elimination of thioformaldehyde from the initially formed adduct<sup>3</sup>.



The dienes **1B,C** (R=iPr) react sluggishly with dienophiles **3** to give adducts **5** in modest yield. The endo/exo selectivity ranges from 3:1 to 1:1. The adducts are stable to the reaction conditions. However, a toluene(*d*<sub>8</sub>) solution of **1B** at 120°C decomposes to unidentified products with a  $t_{1/2}$ =6 days (NMR).



The hydrolyzed (HF-MeCN) adducts are readily desulfurized with W2 Raney nickel in methanol (Scheme 1). The resulting compounds<sup>9</sup> are equivalent to endo Diels-Alder adducts from a *cis*-diene. To compare the reactions of **1B** with an acyclic diene, 1-penten-3-one was converted into **11a**<sup>10,11</sup>. The diene **11a** reacts with **2H** (xylene/50°C, 79%) to provide a single adduct which upon hydrolysis (NaHCO<sub>3</sub>(aq)/THF, 87%) gives **12**<sup>9</sup>. The (*E*) isomer of **11a** does not give a Diels-Alder adduct with **2H**<sup>11</sup>. By contrast, reaction of **11a** with **3K** (CDCl<sub>3</sub>/60°C, 77%) gives a nearly equimolar mixture of the four possible products **13** and **14**<sup>12</sup>. Analogous results were obtained with **11b**.



Scheme 1

In conclusion, 2H-thiopyrans can act as functional equivalents to *cis* -dienes in Diels-Alder reactions. High regioselectivity and good endo selectivity are observed. Further applications of this methodology will be reported in due course.

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### References and Footnotes

1. (a) J. Sauer, *Angew. Chem. Int. Ed.*, **1966**, 5, 211. (b) A. Wasserman, "Diels-Alder Reactions," American Elsevier, New York, **1965**. (c) A.S. Onishenko, *Diene Synthesis*, Daniel Davey, New York, **1964**.
2. R.H. Flemming and B.H. Murray, *J. Org. Chem.*, **1979**, 44, 2280-82.
3. E. Vedejs, J.S. Stults, R.G. Wilde, *J. Am. Chem. Soc.*, **1988**, 110, 5452.
4. cf. S. Danishefsky, T. Kitahara, *J. Am. Chem. Soc.*, **1974**, 96, 7807.
5. The dienes **1B,C,D** were readily obtained in near quantitative yield by reaction of the corresponding enones<sup>6</sup> with a silylating agent (TMSCl-ZnCl<sub>2</sub>, TBDMSOTf, or TIPSOTf) in CH<sub>2</sub>Cl<sub>2</sub> in the presence of Et<sub>3</sub>N. **1B** (R=Me) was purified by distillation (bp 65°C/2 torr, 74%). Other dienes could not be distilled without extensive decomposition and were purified by flash column chromatography (SiO<sub>2</sub> [pretreated with Et<sub>3</sub>N], hexane).
6. (a) The enones corresponding to **1B** and **1C** were prepared by the method of Vedejs: E. Vedejs, T.H. Eberlein, D.J. Mazur, C.K. McClure, D.A. Perry, R. Ruggeri, E. Schwartz, J.S. Stults, D.L. Varie, R.G. Wilde, and S. Wittenberger, *J. Org. Chem.*, **1986**, 51, 1556. (b) The enone corresponding to **1D** was prepared from 4-thiacyclohex-2-enone<sup>6a</sup> by addition of thiophenol followed by NCS oxidation (overall yield, 40%). cf. V.K. Kansal and R.J.K. Taylor, *J. Chem. Soc. Perkin Trans. I*, **1984**, 703.
7. Diene **1E** was prepared as follows: reaction of 1,3-dimethoxy-1-trimethylsilyloxy-1,3-butadiene (J. Savard and P. Brassard, *Tetrahedron*, **1984**, 40, 3455) with thioformaldehyde according to the method of Vedejs<sup>6a</sup> followed by work-up with acidic methanol gave 3-methoxy-6-thiacyclohex-2-enone (50%). Treatment with LDA (2eq.) followed by TIPSOTf gave **1E**. This diene was very unstable and was not further purified.
8. The stereochemistry was apparent from analysis of the <sup>1</sup>H NMR spectra. Especially useful was the consistent presence of <sup>4</sup>J coupling (W-coupling) between mutually exo protons. NOE experiments confirmed the stereochemical assignment.
9. The stereochemical assignment was based on the analysis of the coupling constants for H<sub>A</sub>-H<sub>B</sub> and H<sub>B</sub>-H<sub>C</sub>. cf. S. Danishefsky, C.F. Yan, and P. M. McCurry, Jr., *J. Org. Chem.*, **1977**, 42, 1819.
10. An 85:15 mixture of **11a** and the corresponding (E) isomer was obtained. cf. (a) P. Cazeau, F. Duboudin, F. Moulines, O. Babot, and J. Dunogues, *Tetrahedron*, **1987**, 43, 2089. (b) C. Girard and J.-M. Conia, *J. Chem. Res. (M)*, **1978**, 2351-85. (c) S. Danishefsky and C. F. Yan, *Synth. Commun.*, **1978**, 8, 211.
11. Conia<sup>10b</sup> and Cazeau<sup>10a</sup> report the major product to be the (E)-isomer. The basis for the stereochemical assignment is not reported. While the <sup>1</sup>H NMR spectrum of our product is similar to that reported<sup>10</sup>, we believe the major product is the (Z) isomer. Although NOE experiments proved to be inconclusive, the (Z) stereochemistry is consistent with the <sup>13</sup>C NMR spectrum; major isomer: δ 149.7(s), 135.5(d), 111.3(t), 110.2(d), 11.6(q), 0.59(q); minor isomer: δ 148.1(s), 129.2(d), 113.8(t), 107.4(d), 11.4(q), 0.13(q). cf. C.H. Heathcock, C.T. Buse, W.A. Kleschick, M.C. Pirrung, J.E. Sohn, and J. Lampe, *J. Org. Chem.*, **1980**, 45, 1066. A Diels-Alder reaction of the diene mixture with excess N-phenylmaleimide (**2H**) conducted in an NMR tube reveals that only the major isomer is consumed (prolonged heating does not consume the minor isomer). The stereochemistry of the resulting product (**12**) is consistent with an endo reaction of a (Z)-diene.
12. Poor regioselectivity with **11a** has been observed: D.J. Ackland and J.T. Pinhey, *J. Chem. Soc. Perkin Trans. I*, **1987**, 2689.