## Diels-Alder Reactions of $\alpha$ , $\beta$ -Unsaturated Thioesters and $\alpha$ , $\beta$ -Unsaturated Selenoesters

Chang-Ho Byeon, Cheng-Yi Chen, David A. Ellis, David J. Hart\* and Jing Li Department of Chemistry, The Ohio State University, 100 W. 18th Ave. Columbus, Ohio 43210, USA *Received 14 November 1997* 

**Abstract:**  $\alpha,\beta$ -Unsaturated thioesters and selenoesters serve as dienophiles in Diels-Alder reactions with a variety of 1,3-dienes. Good levels of regioselectivity are obtained with unsymmetrical dienes when Lewis acid promoters are used. Thioesters and selenoesters are more reactive than the corresponding methyl esters based on competition experiments with cyclopentadiene.

Only a few examples of Diels-Alder reactions in which  $\alpha,\beta$ -unsaturated thioesters serve as dienophiles have been reported<sup>1-5</sup> and the use of  $\alpha,\beta$ -unsaturated selenoesters as dienophiles has not been described. During the course of two alkaloid total syntheses, we found  $\alpha,\beta$ -unsaturated thioesters to be useful in situations where the corresponding esters lacked reactivity needed to participate in Diels-Alder reactions.<sup>3,4</sup> Because of their potential for use in synthesis and the limited attention they have received to date, we have conducted a systematic study of Diels-Alder reactions of selected  $\alpha,\beta$ -unsaturated thioesters and related  $\alpha,\beta$ -unsaturated selenoesters. The results are reported herein.

Thioesters and selenoesters 1-4 were selected for study and prepared as follows. Treatment of crotonyl chloride with one equivalent of thiophenol or selenophenol in the presence of pyridine gave 1 (45%) and 2 (48%), respectively. Similar treatment of methyl fumaroyl chloride with thiophenol or selenophenol provided 3 (mp 70-71°C) and 4 (mp 62-65°C), in 46% and 45% yields, respectively. Cycloaddition reactions of these dienophiles were examined with isoprene (5), piperylene (6), 2-trimethylsiloxy-1,3-butadiene (7), and cyclopentadiene (8). Each cycloaddition was examined under three conditions: thermal, using a soluble Lewis acid promoter (EtAlCl2 or TiCl<sub>4</sub>), and using a solid supported Lewis acid promoter (SiO<sub>2</sub>-Et<sub>2</sub>AlCl).<sup>6</sup> The results are documented in Tables 1-4.



Table 1 shows that thermal reactions between 1-4 and isoprene (Condition A) show little regioselectivity as expected.<sup>7-8</sup> Regioselectivity improves to useful levels upon use of soluble Lewis acid promoters (Condition B).<sup>7</sup> Most notable is that the thioester and selenoester groups in **3** and **4** direct the course of the cycloaddition rather than the carbomethoxy group.<sup>9</sup> Finally, the solid supported Lewis acid (Condition C) provides useful levels of reactivity with crotonic acid derivatives **1** and **2**, but is ineffective with fumaric acid derivatives **3** and **4**.

Table 2 shows that thermal reactions between **1-4** and piperylene afford a mixture of regioisomeric endo and exo cycloadducts.<sup>10</sup> As with isoprene, the use of either soluble or solid supported Lewis acids improves both regioselectivity and stereoselectivity with dienophiles **1** and **2**. Dienophiles **3** and **4** do not respond well to Lewis acids, however, as four isomeric cycloadducts are obtained.

Table 3 shows that thermal and soluble Lewis acid promoted reactions of **1** and **2** with 2-trimethysiloxy-1,3-butadiene give good yields of cyclohexanones with excellent regioselectivity after a hydrolytic work-up.<sup>11</sup> On the other hand dienophiles **3** and **4** show good regioselectivity only in the presence of soluble Lewis acid promoters. Once again, the thioester and selenoester groups direct the regiochemical course of the

Table 1. Cycloadditions Between Isoprene (5) and Dienophiles 1-4						
Me		ditions				
5			р		m	
Dienophile	X	Y	Conditions <sup>a</sup>	Yield <sup>b</sup>	Ratio (p:m) <sup>c</sup>	
1	COSPh	Me	A (Thermal)	80%	63:37	
1	COSPh	Me	B (EtAlCl <sub>2</sub> )	70%	88:12	
1	COSPh	Me	C (SiO2-Et2AlCl)	87%	90:10	
2	COSePh	Me	Α	50%	60:40	
2	COSePh	Me	B (EtAlCl <sub>2</sub> )	82%	88:12	
2	COSePh	Me	С	58%	88:12	
3	COSPh	$CO_2Me$	Α	82%	50:50	
3	COSPh	$\rm CO_2Me$	B (TiCl <sub>4</sub> )	74%	95:5	
3	COSPh	CO <sub>2</sub> Me	С	97%	54:46	
4	COSePh	CO <sub>2</sub> Me	Α	81%	55:45	
4	COSePh	$\rm CO_2Me$	B (TiCl <sub>4</sub> )	77%	100:0	
4	COSePh	$\rm CO_2Me$	С	88%	46:54	

 ${}^{a}A = 20$  equiv of 5 in xylene in a sealed tube in an oil bath at 190-195°C for 24 h; B = 1.1 equiv of Lewis acid in dichloromethane with 3-5 equiv of 5 at -60°C $\rightarrow$ rt for 2-18 h; C = 400 mg of SiO<sub>2</sub>-Et<sub>2</sub>AlCl/mmol 1-4 in toluene with 3-5 equiv of 5 at rt for 18-60 h. <sup>b</sup>Purified mixture of cycloadducts. <sup>c</sup>Determined by <sup>1</sup>H-NMR analysis of the purified mixture of cycloadducts

Table 2. Cycloadditions Between Piperylene (6) and Dienophiles 1-4

$\int_{6}^{Me} \frac{X}{Cc}$	y enditions	Me a	$     \int_{Y}^{W} \bigvee_{\mathbf{b}}^{\mathbf{Me}} \sum_{\mathbf{b}}^{X} $	Me c	$ \begin{array}{c} Me \\ X \\ X \\ d \end{array} $
Dienophile	Х	Y	<b>Conditions</b> <sup>a</sup>	Yield <sup>b</sup>	Ratio (a:b:c:d) <sup>c</sup>
1	COSPh	Me	A (Thermal)	77%	35:54:11:0 <sup>d</sup>
1	COSPh	Me	B (EtAlCl <sub>2</sub> )	70%	83:17:0:0
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1	COSPh	Me	C (SiO <sub>2</sub> -Et <sub>2</sub> AlCl)	60%	85:15:0:0	
2	COSePh	Me	Α	38%	34:56:10:0 <sup>d</sup>	
2	COScPh	Mc	B (EtAlCl <sub>2</sub> )	39%	80:20:0:0	
2	COSePh	Me	С	75%	87:13:0:0	
3	COSPh	CO <sub>2</sub> Me	Α	96%	29:27:24:20	
3	COSPh	CO <sub>2</sub> Me	B (EtAlCl <sub>2</sub> )	77%	67:14:16:3	
3	COSPh	CO <sub>2</sub> Me	С	79%	56:16:24:5	
4	COSePh	CO <sub>2</sub> Me	Α	60%	30:30:20:20	
4	COSePh	CO <sub>2</sub> Me	B (EtAlCl <sub>2</sub> )	72%	60:14:21:5	
4	COSePh	CO <sub>2</sub> Me	С	68%	52:18:25:5	

<sup>a</sup>A = 5-10 equiv of **6** in xylene in a sealed tube in an oil bath at 185-195°C for 24-48 h; B = 1.1 equiv of Lewis acid in dichloromethane with 3-5 equiv of **6** at -20°C $\rightarrow$ rt for 8-40 h; C = 400 mg of SiO<sub>2</sub>-Et<sub>2</sub>AlCl/mmol **1-4** in toluene with 3-4 equiv of **6** at rt for 15-72 h. <sup>b</sup>See Table 1. <sup>c</sup>See Table 1. <sup>d</sup>Structures of **c** and **d** may be reversed

cycloadditions. Also, the solid supported Lewis acid (SiO<sub>2</sub>- $Et_2AlCl$ ) destroyed diene 7 and no cycloadducts were obtained.

Table 4 indicates that thermal reactions of cyclopentadiene with 1-4 show little endo-exo selectivity, but the situation improves in the presence of Lewis acid promoters.<sup>12</sup> For example, titanium tetrachloride improves selectivity to useful levels with all four dienophiles, whereas  $SiO_2$ -Et<sub>2</sub>AlCl improves selectivity in reactions of 1 and 2, but is ineffective in reactions of 3 and 4.

One feature of thioesters and selenoesters as dienophiles is that they are more reactive than normal esters. For example, when a 10-fold excess of dimethyl fumarate (9) and dithioester 10 (mp 135-136°C) were allowed



<sup>a</sup>A = 4-7 equiv of 7 in xylene in a sealed tube in an oil bath at 185-195°C for 24 h; B = 1.1 equiv of Lewis acid in dichloromethane with 2-3 equiv of 7 at -25°C for 8-10 h; C = see Table 1. <sup>b</sup>See Table 1. <sup>c</sup>See Table 1

Table 4. Cycloadditions Between Cyclopentadiene (8) and Dienophiles 1-4



 ${}^{s}A = 7$  equiv of **8** in xylene in a sealed tube in an oil bath at 100°C for 24 h; B = 1.1 equiv of Lewis acid in dichloromethane with 3 equiv of **8** at -78 $\rightarrow$ -25°C for 15-30 min; C = 400 mg of SiO<sub>2</sub>-Et<sub>2</sub>AlCl/mmol 1-4 in toluene with 3-4 equiv of **6** at -78°C $\rightarrow$ rt for 1-50 h. bSee Table 1. See Table 1

to compete for a limiting amount of cyclopentadiene, cycloadduct 12 was obtained along with only trace amounts of 13. A competition between dimethyl fumarate and diselenoester 11 (mp 121-122°C) also gave 14 and only a trace of 13.<sup>13</sup>



Another useful feature of thioesters and selenoesters as dienophiles is that the chemistry of these functional groups differs from the chemistry

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that the chemistry of these functional groups differs from the chemistry of esters. This can be put to good use. For example in a synthesis of himbacine, a thioester cycloaddition was followed by its reduction to an alcohol using RaNi, without reduction of an appended lactone.<sup>4</sup> To further demonstrate the utility of this difference in reactivity, the cycloadduct derived from isoprene and selenoester **4** was treated with tri-*n*-butyltin hydride and AIBN to provide keto ester **15** in 56% yield along with 16% of aldehyde **16**.<sup>14</sup> This establishes **4** as a reverse regiochemistry acrylate equivalent in Diels-Alder reactions.<sup>15</sup> Finally, treatment of the cycloadduct derived from isoprene and thioester **3** with sodium borohydride in ethanol, gave hydroxy ester **17** in 74% yield, establishing another reverse regiochemistry equivalent. It is our hope that these studies will encourage others to use thioesters and selenoesters as dienophiles in appropriate situations.

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- 8. The major product (**p**) from each reactant pair was isolated and characterized by <sup>1</sup>H and <sup>13</sup>C NMR, IR and MS. The presence of minor cycloadducts (**m**) was inferred from signals in the NMR spectra of purified product mixtures [for example the allylic methyl group (reactions of **1-2**) and the methines adjacent to the thioester and/or ester groups (reactions of **1-4**)]. The regiochemistry in the reactions of **1** and **2** with **5** are based on the well-known behavior of crotonate-isoprene cycloadditions.<sup>7</sup> INADEQUATE (<sup>13</sup>C-<sup>13</sup>C correlation) experiments were used to establish regiochemistry in the cycloaddition between **3** and **5**.
- For another fumaric acid derivative that shows selective complexation with a Lewis acid see Maruoka, K.; Saito, S.; Yamamoto, H. J. Am. Chem. Soc. 1992, 114, 1089.
- 10. Pure samples of **a** and **b** were obtained from reactions involving **1** and **2**. Their stereochemistry was assigned on the basis of the coupling constants of the methine adjacent to the carbonyl group [dd (J = 10, 5 Hz) for **a** and t (J = 10 Hz) for **b**]. The third isomer (stereochemistry unknown) was detectable in the <sup>1</sup>H-NMR of the purified mixture. Product ratios in reactions of **3** and **4** were determined by integration of their respective methyl doublets, which were clearly separated ( $\delta$  0.97, 1.17, 0.90 and 1.05 for **a**-**d** respectively). Pure samples of **a** and **b** were isolated and their structures and stereochemistry assigned using a combination of coupling constant data, INADEQUATE ( ${}^{13}C{}^{-13}C$  correlation)

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experiments, iodolactonization experiments, and chemical correlation with piperylene-dimethyl fumarate cycloadducts.

- 11. Pure samples of the major products (**p**) from each of the four cycloaddition pairs were isolated and characterized by <sup>1</sup>H and <sup>13</sup>C NMR, IR and MS. Signals due to minor cycloadducts (**m**) were not apparent in the reactions of **1** and **2**. They were clearly present in the NMR spectra (CO<sub>2</sub>Me) of purified reaction products derived from **3** and **4**. INADEQUATE (<sup>13</sup>C-<sup>13</sup>C correlation) experiments were used to establish regiochemistry in the cycloaddition between **3** and **7**.
- 12. Pure samples of all products were isolated except for the *exo*-adduct in the reaction of **3**. A one-pot hydrolysis-

mercurilactonization reaction (HgCl<sub>2</sub>, CaCO<sub>3</sub>, CH<sub>3</sub>CN, H<sub>2</sub>O) established the structures of the *endo* adducts from 1 and 3. The carboxylic acid derived from the *exo*-adduct with 3 was isolated and characterized when this sequence was applied to a mixture of *endo* and *exo* cycloadducts.

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