

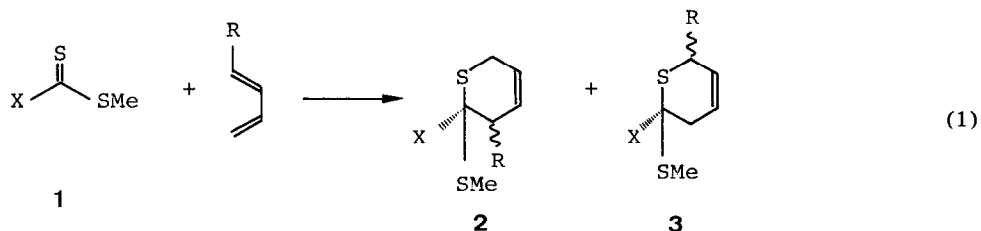
N-Methyldithiophthalimide as a Highly Regioselective Hetero Dienophile in Diels-Alder Reaction

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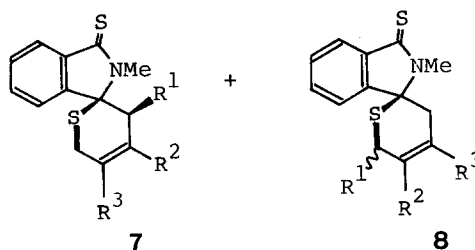
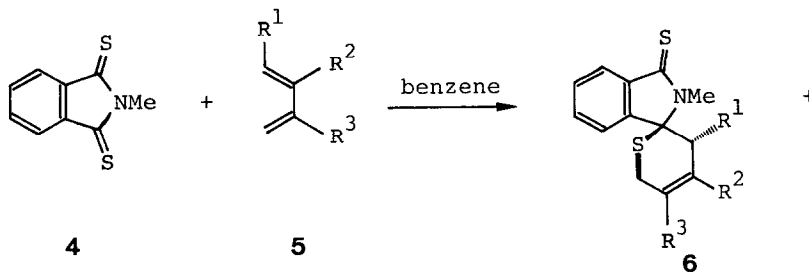
Summary: N-Methyldithiophthalimide serves as a very reactive dienophile and reacts with 1,3-dienes at room temperature to give Diels-Alder products in very high regioselectivity. Stereoselectivity and retro-Diels-Alder of products are referred to.

Because of the synthetic utility, Diels-Alder reaction involving hetero dienophiles is a major current topic in organic chemistry.<sup>1</sup> Compared with the activated carbonyl<sup>2</sup> and imino Diels-Alder reactions,<sup>3</sup> the regio- and stereoselectivities of the thiocarbonyl Diels-Alder have not been fully characterized yet. Vyas et al.<sup>4</sup> and Vedejs et al.<sup>5</sup> have found that the dithioester 1 with electron-withdrawing substituents (X = COR, CN) reacts with unsymmetrically substituted dienes to furnish the regioisomer 2 in high selectivity. In contrast to these, Beslin et al.<sup>6</sup> have reported that methyl dithioacetate (1, X = Me) reacts with dienes to give predominantly the reversed type of regioisomer 3 (eq 1). The Diels-Alder reaction with thioaldehydes shows the similar trend of regioselectivity.<sup>7</sup>



Here we report that N-methyldithiophthalimide 4 serves as a very reactive thiodienophile and reacts with 1-substituted and 1,2- and 1,3-disubstituted 1,3-dienes to give one regioisomer 6 (and 7) exclusively. Our results together with the reaction conditions of the Diels-Alder reaction of 4 with 1,3-dienes of a wide structural variety are summarized in Table I. Reactions were usually performed with 4 (1 mmol) and a diene (10 mmol) in 10 ml of benzene in the presence of air. In every case, the yield was almost quantitative. The conversions and the reaction times in entries 1 - 6 reveal that the reaction is significantly

accelerated by the methyl substituent on 1,3-diene.



(2)

While 4 reacted with isoprene with moderate regioselectivity in favor of the regioisomer 8 ( $\frac{8}{6} = 2.5 : 1$ ), 4 reacted with various kinds of 1-substituted and 1,2- and 1,3-disubstituted 1,3-dienes to give single regioisomers exclusively (as a stereoisomeric mixture of 6 and 7). These regioselectivities are the same pattern as observed with the activated thiodienophiles (e.g., 1; X = COR, CN and activated thioaldehydes)<sup>4,5,7</sup> and quite the reverse of those observed with carbonyl and imino-dienophiles.<sup>2,3,6</sup>

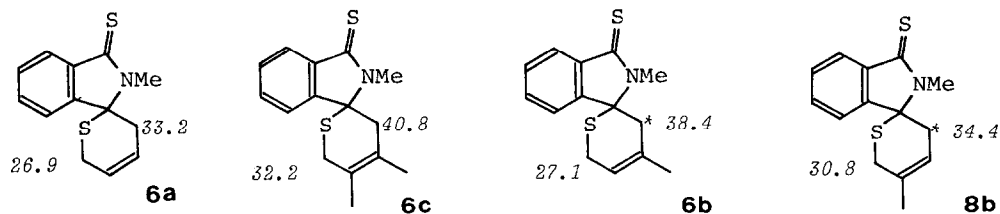


Fig. 1. Selected  $^{13}\text{C}$  NMR Data (ppm).

The structure of the adducts of 4 and isoprene, 8b and 6b ( $R^1 = \text{H}$ ,  $R^2 = \text{Me}$ ,  $R^3 = \text{H}$ ), was determined on the basis of  $^{13}\text{C}$  and  $^1\text{H}$  NMR analysis. In the  $^{13}\text{C}$  NMR spectra systematic down-field shifts of resonances were observed for the two kinds of methylene carbons depending on the positions of methyl substituent(s).<sup>8</sup> Selected data are listed in Fig 1. In the  $^1\text{H}$  NMR spectrum (400 MHz,  $\text{CDCl}_3$ ) of 8b, the diastereotopic methylene protons

(asterisked in Fig I) resonated at 2.52 (d.d.d.d,  $J = 16.7, 5.1, 3.4, 1.7$  Hz, 1 H) and 2.76 ppm (d.d.d.d,  $J = 16.7, 8.1, 4.0, 2.0$ ); both signals collapsed to a d.d.d ( $J = 16.7, 3.4, 1.7$  Hz) and d.d.d ( $J = 16.7, 4.0, 2.0$  Hz), respectively, upon irradiation of the olefinic proton (5.73 ppm). The shapes of the corresponding methylene protons signals (2.41 (br. d,  $J = 16.0$  Hz, 1 H) and 2.70 ppm (br. d,  $J = 16.0$  Hz, 1 H)) of  $\underline{6b}$  remained almost unchanged upon irradiation of the olefinic proton (5.94 ppm).

Table I. Diels-Alder Reaction of  $\underline{4}$  with 1,3-Dienes  $\underline{5}$ .

entry	diene <sup>a</sup>			reaction conditions <sup>b</sup> (conversion %)	yield of product (%) <sup>c</sup> (ratio of products)
	R <sup>1</sup>	R <sup>2</sup>	R <sup>3</sup>		
1	$\underline{5a}$ : H	H	H	rt, 5 d (31)	$\underline{6a}$ : 87
2	$\underline{5b}$ : H	Me	H	rt, 4 d (60)	$\underline{8b}$ + $\underline{6b}$ : 98 (2.5 : 1)
3	$\underline{5c}$ : H	Me	Me	rt, 4 d (85)	$\underline{6c}$ : 100
4	$\underline{5d}$ : Me	H	H	rt, 4 d (62)	$\underline{6d}$ + $\underline{7d}$ : 100 (1.4 : 1)
5	$\underline{5e}$ : Me	H	Me	rt, 2 d (100)	$\underline{6e}$ + $\underline{7e}$ : 100 (1.4 : 1)
6	$\underline{5f}$ : Me	Me	H	rt, 2 d (98)	$\underline{6f}$ + $\underline{7f}$ : 100 (2 : 1)
7	$\underline{5f}$ : Me	Me	H	refl, 2 h (100)	$\underline{6f}$ + $\underline{7f}$ : 100 (2 : 1)
8	$\underline{5g}$ : Ph	Me	H	rt, 12 h (100)	$\underline{6g}$ + $\underline{7g}$ : 100 (2 : 1)
9	$\underline{5g}$ : Ph	Me	H	refl, 0.6 h (100)	$\underline{6g}$ + $\underline{7g}$ : 100 (2 : 1)
10	$\underline{5g}$ : Ph	Me	H	refl, 16 h (100)	$\underline{6g}$ + $\underline{7g}$ : 82 (2 : 1)
11	$\underline{5h}$ : Me	Ph	H	refl, 0.6 h (100)	$\underline{6h}$ + $\underline{7h}$ : 100 (2 : 1)
12	$\underline{5i}$ : Ph	Ph	H	refl, 0.6 h (100)	$\underline{6i}$ + $\underline{7i}$ : 100 (1.9 : 1) <sup>d</sup>

a)  $\underline{5f}$  (E/Z = 5 : 1, prepared according to the method reported).<sup>10</sup>  $\underline{5g}$  (E/Z = 76 : 24, prepared by dehydration of 3-methyl-4-phenyl-3-buten-2-ol/  $\text{KHSO}_4$ ).  $\underline{5h}$  (E/Z = 83 : 17, prepared by dehydration of 3-phenyl-4-methyl-3-buten-2-ol/  $\text{KHSO}_4$ ). b) Except for entry 8,  $\underline{4}$  (1 mmol) and diene (10 mmol) in benzene (10 mL).<sup>4</sup> Entry 8:  $\underline{4}$  (1 mmol) and diene (15 mmol) in benzene (0.5 mL). rt = room temperature, refl = reflux, d = day(s), h = hour(s). c) Isolated yield based on conversion. d) The same ratio was obtained independently of the stereochemical purity of  $\underline{5i}$  (pure E and E/Z = 3 : 1)

There seems to be a general trend between the stereoselectivity and the substitution pattern of 1,3-dienes. With 1-methyl and 1,3-dimethylbutadienes a mixture of  $\underline{6}$  and  $\underline{7}$  was obtained in a ratio of 1.4 : 1. With 1,2-disubstituted dienes,  $\underline{6}$  and  $\underline{7}$  were obtained in a ratio

of 2 : 1. The structure determination of  $\overset{\sim}{6}g,i$  and  $\overset{\sim}{7}g,i$  rests on the large up-field shift of the phenyl ring proton signal ortho to the spiro center in  $\overset{\sim}{6}g,i$  and the N-methyl protons signals in  $\overset{\sim}{7}g,i$ , both of which may be caused by the shielding effect arising from the neighbouring R<sup>1</sup> phenyl substituent (e.g.,  $\overset{\sim}{6}g$ : 6.28 (d, J = 7.3 Hz, 1 H), 3.66 ppm (s, 3 H).  $\overset{\sim}{7}g$ : 2.70 ppm (s, 3 H)).<sup>9</sup>

The Diels-Alder product  $\overset{\sim}{6}g$  is stable as a solution in d<sub>1</sub>-chloroform at room temperature, while at 90 °C in d<sub>8</sub>-toluene under argon,  $\overset{\sim}{6}g$  underwent a facile retro-Diels-Alder reaction and a stationary state was achieved after 4 hr, giving a mixture of  $\overset{\sim}{6}g$ ,  $\overset{\sim}{7}g$ , and  $\overset{\sim}{4}$  in a ratio of 2 : 1 : 2.2, as judged from the N-methyl signals intensity in the <sup>1</sup>H NMR spectra.<sup>11</sup> These observations together with the results in entries 8 (kinetic) and 10 (thermodynamic) clearly indicate that both the kinetic and the thermodynamic ratios of  $\overset{\sim}{6}g$  to  $\overset{\sim}{7}g$  are the same.

Finally it is worth noting that the exclusive formation of  $\overset{\sim}{6}g$  and  $\overset{\sim}{7}g$  in entry 10 indicates that the regioselectivity in the present Diels-Alder reaction is much higher than it appears, otherwise the apparently thermodynamically more stable  $\overset{\sim}{8}g$  may accumulate under this thermodynamic conditions.<sup>12</sup>

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- The retro D-A of  $\overset{\sim}{6}g$  was further confirmed by the cross-over experiments: 1,3-pentadiene (50 fold excess) and  $\overset{\sim}{6}g$  were heated at 90°C in toluene to provide mixtures of  $\overset{\sim}{6}g$  +  $\overset{\sim}{7}d/\overset{\sim}{6}g$  +  $\overset{\sim}{7}g/\overset{\sim}{4}$  = 53 : 46 : 1 and 87 : 7 : 6 after 0.5 and 2.2 h, respectively.
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