Highly Regio-, Stereo-, and Chemoselective Diels–Alder Reaction of Monothiomaleimide, an Ambident C=S and C=C Dienophile

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The thiocarbonyl group of monothiomaleimide **1** serves as a more reactive dienophile than the electron-deficient C=C double bond in the same molecule for the Diels–Alder reaction with dienes **2c–g** and provides *ortho-endo* products **3** exclusively or predominantly over the other possible adducts **4–10**.

The Diels–Alder[1] and hetero-Diels–Alder reactions[2] are among the most powerful carbon–carbon and carbon–heteroatom bond-forming processes and have long been of interest to many synthetic and theoretical organic chemists. Despite extensive studies, however, the regio- and stereochemical behaviour of thioaldehydes and thioketones in the Diels–Alder reaction are still ill-defined.[3]

The thiocarbonyl group of acid derivatives (*e.g.* dithioester, thioamide) is less reactive[4] and generally can serve as a dienophile, if activated as α-oxo[5] or anhydride derivatives.[6] In α,β-unsaturated systems, it may react as a component of a diene.[7] Here we report that the thiocarbonyl group of *N*-substituted monothiomaleimide **1**, doubly activated with imide and vinylogous oxo moieties, serves as a more reactive dienophile than the electron-deficient C=C double bond present in the same molecule and displays high regio- (*o*- and *p*-) and stereo-selectivities (*endo*) towards 1,3-dienes. These selectivities rank as some of the highest among thiocarbonyl Diels–Alder reactions of acid derivatives.[6]

N-Substituted monothiomaleimides (**1**, R = Ph, *p*-$O_2NC_6H_4$, *p*-$MeOC_6H_4$, $PhCH_2$) react with dienes **2a–g** at room temperature and provide the addition products **3–6** in good yields (Scheme 1, Table 1). *N*-(*p*-Nitrophenyl)monothiomaleimide (**1**, R = *p*-$O_2NC_6H_4$) is too unstable to isolate and is subjected to reaction without rigorous purification (run 7, Table 1).

The chemoselectivity between the C=S and C=C double bonds of **1** changes dramatically depending on the substitution pattern of the dienes, and in general the ratio of the C=S adducts (**3** + **4**) to C=C adducts (**5** + **6**) increases with an increase in the π-conjugation of 1,3-dienes with their substituents, from 45/55 for **2a,b** (runs 1–2) to 100/0 for **2e–g** (runs 8–11). The chemoselectivity is also affected by the type of *N*-substituent; the stronger the electron attraction of the substituents, the greater the C=S selectivity (runs 3–7).

The thiocarbonyl group of **1** shows unique regio- and stereo-selectivities. As for the regioselectivity, the *o,p*-orientation products **3** (and **4**)[8] are formed exclusively. The *m*-products **7** (and **8**) cannot be detected at all for dienes. The specific formation of the *p*-product **3b** in the reaction with isoprene **2b** is very impressive (run 2 and footnote f in Table 1), since **2b** is notorious for providing *m*- and *p*-mixtures with a slight preference for the *p*-isomers.[3l,9] Indeed, the C=C adducts, **5b** and **6b**, were formed as a 1 : 1 mixture (run 2, Table 1). As for the stereoselectivity, the thiocarbonyl group of **1** is highly *endo*-selective, providing **3** exclusively (runs 6–7, 9–11) or highly selectively (runs 3–5, 8). Interestingly, a significant increase in the *endo*/*exo* ratios (**3**/**4**) is observed with an increase in electron attraction of the *N*-substituents (runs 3–5).

The C=C double bond of **1** furnishes *endo*-addition products as a mixture of regioisomers **5** and **6**. No *exo*-adducts **9** and **10** are formed. As judged from a preferential formation of **5** over **6** (runs 3–5), the thiocarbonyl group, rather than the carbonyl group, seems to be operating as an *ortho*-directing functionality.

The structures of **3–6** were deduced from ^1H and ^{13}C NMR spectra.† The key data for **3c–6c** and the related compounds are shown in Fig. 1. The structures of **3d–g** were elucidated by similar procedures. The ^1H and ^{13}C NMR spectra of **6c** (R = Ph) are identical to those of the product obtained selectively by the thionation of **11**, the Diels–Alder product of 1,3-

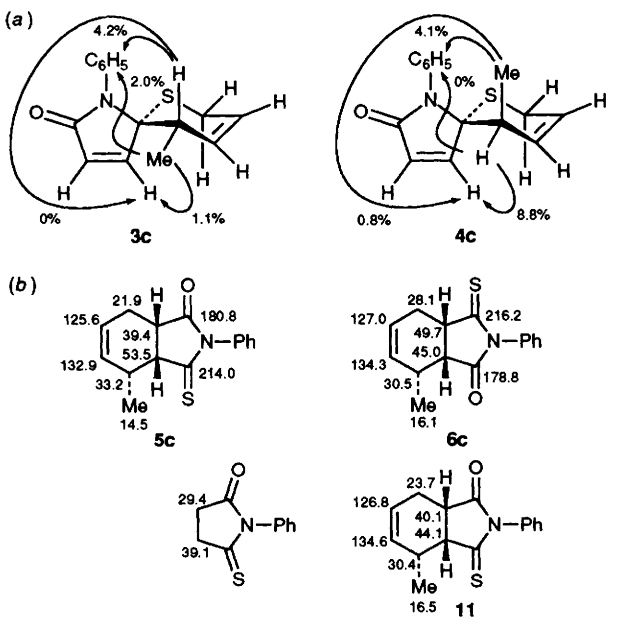
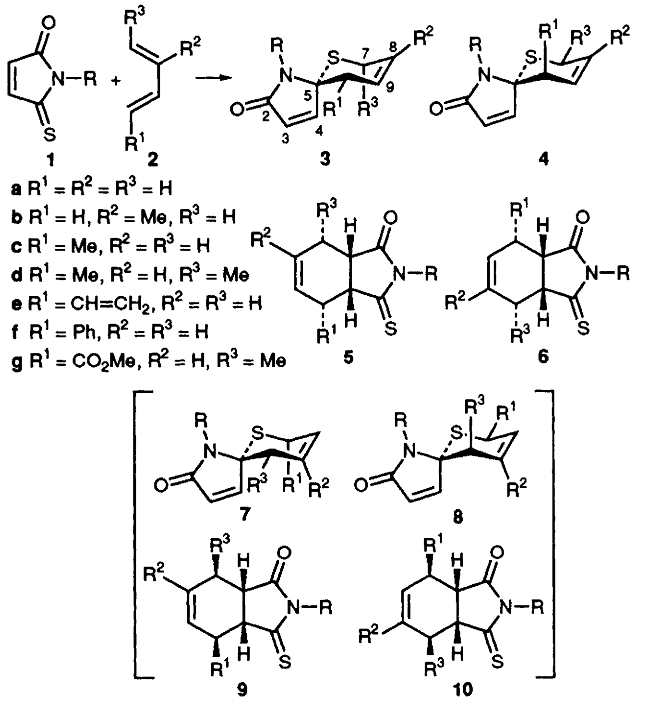


Fig. 1 (*a*) Nuclear Overhauser effects for **3c** and **4c** (R = Ph) (400 MHz ^1H NMR). (*b*) ^{13}C NMR chemical shifts (δ in ppm) for **5c**, **6c** (R = Ph), and the related compounds.



a $R^1 = R^2 = R^3 = H$
b $R^1 = H, R^2 = Me, R^3 = H$
c $R^1 = Me, R^2 = R^3 = H$
d $R^1 = Me, R^2 = H, R^3 = Me$
e $R^1 = CH{=}CH_2, R^2 = R^3 = H$
f $R^1 = Ph, R^2 = R^3 = H$
g $R^1 = CO_2Me, R^2 = H, R^3 = Me$

Scheme 1

Table 1 Diels–Alder reaction of *N*-substituted monothiomaleimide **1** with dienes **2**[a]

					Product ratio		
Run	**1** (R)	Diene **2**	Time[b] (h)	Yield[c] (%)	C=S (**3** + **4**)/ C=C (**5** + **6**)[d]	**3**/**4**[e]	**5**/**6**[e]
1	Ph	**2a**	48	100	45/55	—	—[h]
2	Ph	**2b**	53	84	45/55	—[f]	50/50
3	Ph	**2c**	90	94	71/29	90/10	75/25
4	p-MeOC$_6$H$_4$	**2c**	16	76	62/38	89/11	72/28
5	PhCH$_2$	**2c**	120	61	41/59	76/24	69/31
6	Ph	**2d**	6	87	66/34	100/0	—[h]
7	p-O$_2$NC$_6$H$_4$	**2d**	12	—[g]	73/27	100/0	—[h]
8	Ph	**2e**	2	92	100/0	93/7	
9	Ph	**2f**	1	86	100/0	100/0	
10	Ph	**2g**	20	80	100/0	100/0	
11	p-MeOC$_6$H$_4$	**2g**	15	89	100/0	100/0	

[a] Reaction conditions: **1** (1 mmol) and **2** (10 mmol) in 1 ml of benzene at room temperature under N_2. [b] Approximate time required for the completion of the reaction. [c] Combined isolated yield of **3–6**. [d] Ratio determined from the isolated yield. [e] Ratio determined from ^{1}H NMR spectra (400 MHz). [f] **3** (= **4**) : **7** (= **8**) = 100/0. [g] Yield not determined (see text). [h] **5** = **6**.

pentadiene and *N*-phenylmaleimide, with P_4S_{10}. The structure of **3b** could be resolved using ^{2}D NMR (400 MHz) techniques, including CH COSY and CH COLOC (*e.g.* correlations between C_8–CH_3 and C_7, C_8, C_9; C_7H_2 and C_5, C_8, C_9; $C_{10}H_2$ and C_9).[10]

Extensive studies aimed at rationalizing the unique selectivity and reactivity of **1** delineated here are under progress following both experimental and theoretical lines.[3b]

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Footnote

† All new compounds, the stereoisomers **3** and **4** separately and **5** and **6** as mixtures, showed satisfactory spectral and analytical data.

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