# 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.[3f,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-

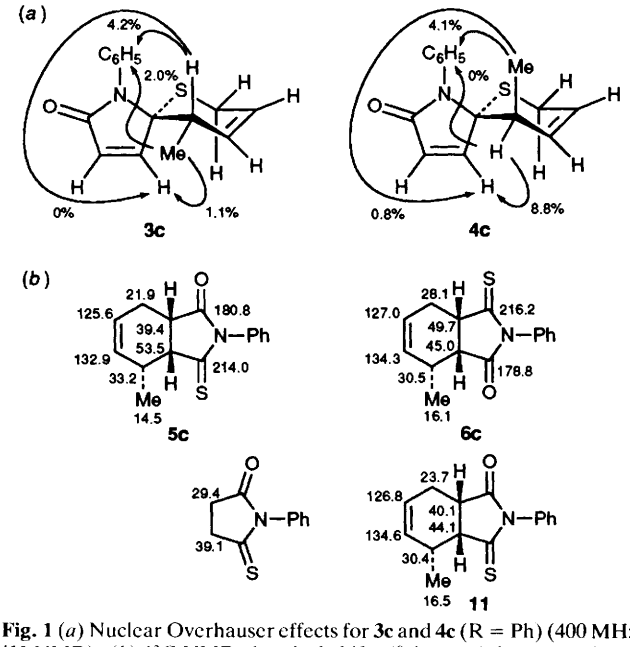
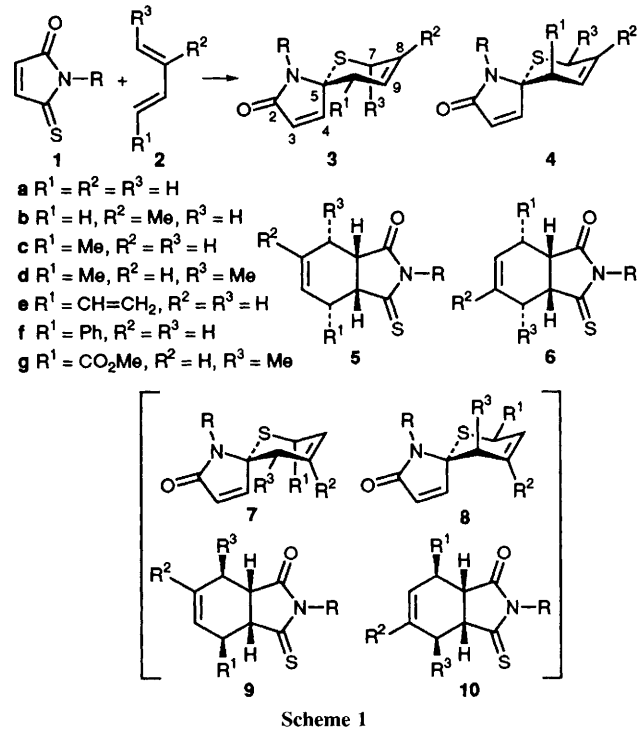



**Fig. 1** (*a*) Nuclear Overhauser effects for **3c** and **4c** (R = Ph) (400 MHz $^1H$ NMR). (*b*) $^{13}C$ NMR chemical shifts (δ in ppm) for **5c**, **6c** (R = Ph), and the related compounds.




**Scheme 1**

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

| Run | 1 (R) | Diene 2 | Time[b] (h) | Yield[c] (%) | Product ratio 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*-$MeOC_6H_4$ | **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*-$O_2NC_6H_4$ | **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*-$MeOC_6H_4$ | **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 $^1H$ 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 $^2D$ 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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