Intramolecular diene-transmissive hetero Diels–Alder reactions of divinyl thioketones

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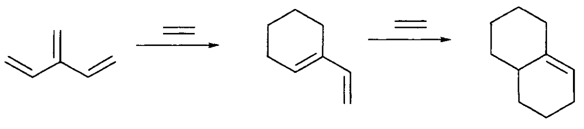
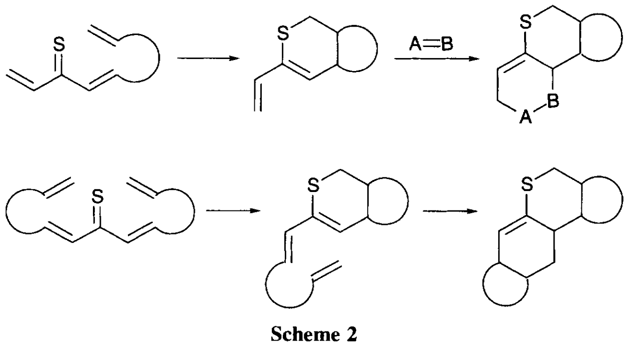
The intramolecular diene-transmissive hetero Diels–Alder reactions of divinyl thioketones to give polyring-fused tetrahydrothiopyrans are described for the first time.

The diene-transmissive Diels–Alder (DTDA) reaction is a useful and attractive synthetic method for construction of ring-fused cyclic compounds, consisting of two sequential (tandem) Diels–Alder (DA) reactions that involve an initial DA cycloaddition of a cross-conjugated triene (or its equivalent) followed by a second DA cycloaddition using the newly formed diene unit (Scheme 1).[1] Tsuge *et al.* have developed the DTDA reactions and the methodology seems to be of great potential in organic synthesis.[1,2] Until our first report in 1990,[3] however, there had been no example reported of the diene-transmissive *hetero* Diels–Alder (DTHDA) reaction despite its high potential for fused heterocyclic ring construction. In that paper we dealt with divinyl thioketones as the heterotrienes in the DTHDA reaction.[3] Recently, Tsuge *et al.* reported the DTHDA reactions of carbotrienes with some reactive diazo-dienophiles,[4] and of divinyl ketones with enamines as the first cycloaddition followed by the second cycloaddition with strong dienophiles such as tetracyanoethylene and triazolinedione.[5] The hitherto reported examples were limited to those involving the intermolecular–intermolecular DTDA or DTHDA processes in reacting with dienophiles.[1–5] We now report for the first time the intramolecular–intermolecular and intramolecular–intramolecular modes of the DTHDA cycloadditions of divinyl thioketones (Scheme 2). The methods were found to be quite useful for the synthesis of polyring-fused heterocycles with high efficiency and predictable stereoselectivity.

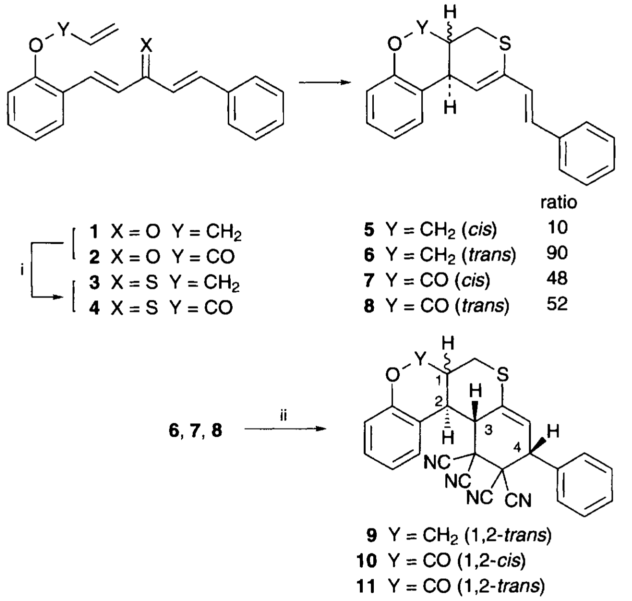
When the ketone **1**† (6.35 g, 21.9 mmol) tethered to an (allyloxy)phenyl group was treated with Lawesson's reagent (L.R., 5.31 g, 13.1 mmol) in benzene (60 cm^3) at 80 °C (Scheme 3, Table 1, run 1), the formed thioketone **3** immediately underwent the initial HDA reaction intramolecularly to afford the cycloadduct **5** + **6** in a high level of regio- and diastereoselectivities (*cis*:*trans* = 10:90).‡,§ In contrast, similar treatment of the ketone **2**† gave the cycloadduct **7** + **8** of the thioketone **4** almost completely nonstereoselectively in a ratio of *cis*:*trans* = 48:52.§ The stereochemical outcome can be explained mainly in terms of the non-bonding interaction, and the second obrital interaction if available, between the diene and internal dienophile moieties in the *endo* and *exo* transition states.[7,8] The diastereoisomerically pure dienes **6**, **7** and **8** thus obtained were treated with tetracyanoethylene (TCNE) in a second DA reaction to give the corresponding cycloadducts **9–11** in good yields (Scheme 3, runs 3–5).§ The 2,3-*trans* configuration of **9–11** suggested that TCNE cycloadded from the less hindered back side of the dienes **6–8**. *N*-Phenyl-



Scheme 1



Scheme 2



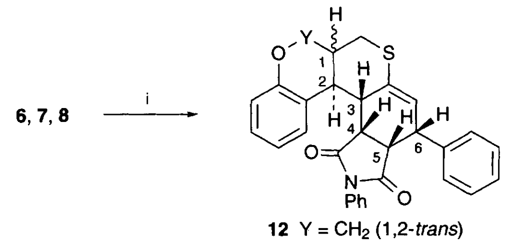
Scheme 3 *Reagents and conditions*: i, L.R., benzene, 80 °C; ii, TCNE, benzene, 80 °C

Table 1 Diene-transmissive hetero Diels–Alder reactions of divinyl thioketones

Run	Diene	Reaction time/h	Cycloadduct (yield, %)[a]
1	**3**	0.3	**5** + **6** (85)
2	**4**	0.5	**7** + **8** (80)
3	**6**	1	**9** (93)
4	**7**	1	**10** (89)
5	**8**	2	**11** (89)
6	**6**	6	**12** (99)
7	**7**	3	**13** (88)
8	**8**	28	**14** (84)
9	**16**	1	**17** + **18** (94)
10	**17**	7	**19** (81)
11	**18**	14	**20** (54)

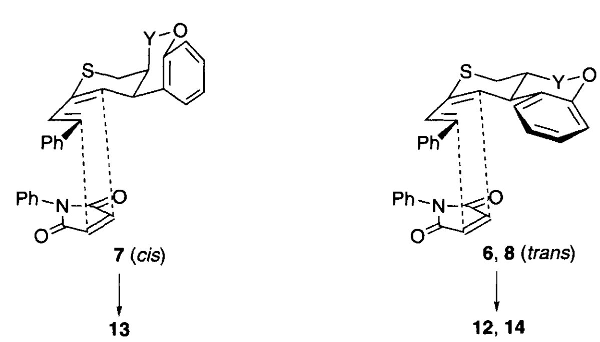
[a] Isolated yield.

maleimide was also able to effect a second cycloaddition with the dienes (Scheme 4, Runs 6–8). The reaction was found to be highly *endo*- and diastereoisoface-selective, giving the single diastereoisomer (**12–14**) in each case.§ Postulated transition-state structures leading to **12–14** are illustrated in Scheme 5. In both transition states, the dienophile attacks the diene in a manner of *endo* orientation from the less congested bottom side. It is also noteworthy that the *cis* configurated isomer **7** reacted faster than the *trans* isomer **8**. The intramolecular–intramolecular DTHDA reaction of **16** could be accomplished by similar treatment of **15**† with L.R. to yield **17** and **18** in a ratio of 33 : 67, followed by simply heating the separated isomers **17** and **18** in xylene at 140 °C to give highly *exo*-selectively the six rings-fused cycloadducts **19** and **20**, respectively (Scheme 6, runs 9–11).§

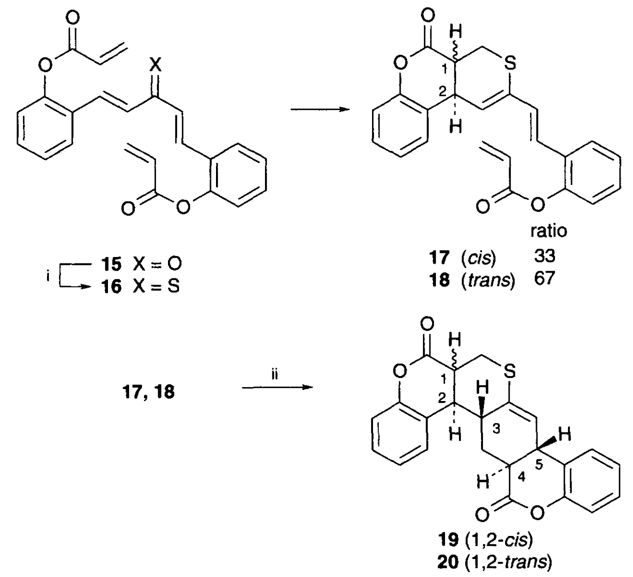


12 Y = CH$_2$ (1,2-*trans*)
13 Y = CO (1,2-*cis*)
14 Y = CO (1,2-*trans*)

Scheme 4 *Reagents and conditions*: i, *N*-phenylmaleimide, xylene, 140 °C



Scheme 5 Transition state structures



Scheme 6 *Reagents and conditions*: i, L.R., benzene, 80 °C; ii, xylene, 140 °C

Footnotes

† The ketones **1**, **2** and **15** were prepared by aldol condensation of salicyl aldehyde with benzal acetone/acetone,[6] followed by introduction of the dienophiles by allylation/acrylation, respectively.

‡ We have previously reported single intramolecular HDA reactions of α,β-unsaturated thioketones, the *endo*/*exo*-diastereoselectivity of which largely depended upon the substituents.[7]

§ The stereochemistry was determined on the basis of ^{1}H NMR spectroscopy. *Selected data* for **6**: mp 130–132 °C; *m*/*z* 306 (M$^+$, 100%); HRMS, found M$^+$ 306.1101 $C_{20}H_{18}OS$ requires *M* 306.1079; ν_{max} (KBr)/cm^{-1} 1584; δ_H (500 and/or 270 MHz, CDCl$_3$) 2.28 (ddddd, 1 H, *J* 11.2, 11.2, 11.2, 3.6 and 3.6 Hz, 1-H$_{ax}$), 2.80 (dd, 1 H, *J* 11.2 and 11.2 Hz, SCH$_{ax}$), 2.90 (dd, 1 H, *J* 11.2 and 3.6 Hz, SCH$_{eq}$), 3.52 (dd, 1 H, *J* 11.2 and 3.0, 2-H$_{ax}$), 3.82 (dd, 1 H, *J* 11.2 and 11.2 Hz, OCH$_{ax}$), 4.34 (dd, 1 H, *J* 11.2 and 3.6 Hz, OCH$_{eq}$), 6.35 (d, 1 H, *J* 3.0 Hz, =CH), 6.72 (d, 1 H, *J* 16.2 Hz, =CH), 6.82 (d, 1 H, *J* 16.2 Hz, =CH) and 6.92–7.43 (m, 9 H, ArH). For **11**: mp 200–201 °C; *m*/*z* 448 (M$^+$, 0.1%), 320 (M$^+$ − TCNE, 100%); HRMS, found M$^+$ 448.1000 $C_{26}H_{16}O_2N_4S$ requires *M*, 448.0996; ν_{max}(KBr)/cm^{-1} 1760 (CO) and 2256 (CN); δ_H 3.06 (dd, 1 H, *J* 12.2 and 11.2 Hz, SCH$_{ax}$), 3.14 (ddd, 1 H, *J* 11.2, 11.2 and 2.6 Hz, 1-H$_{ax}$), 3.28 (dd, 1 H, *J* 12.2 and 2.6 Hz, SCH$_{eq}$), 3.64 (dd, 1 H, *J* 11.2 and 11.2 Hz, 2-H$_{ax}$), 4.08 (ddd, 1 H, *J* 11.2, 2.6 and 2.6 Hz, 3-H$_{ax}$), 4.30 (dd, 1 H, *J* 2.6 and 2.6 Hz, 4-H), 6.69 (dd, 1 H, *J* 2.6 and 2.6 Hz, =CH) and 7.25–7.57 (m, 9 H, ArH). For **19**: mp 268–269 °C; *m*/*z* 390 (M$^+$, 100%); HRMS, found M$^+$ 390.0913 $C_{23}H_{18}O_4S$ requires *M*, 390.0926; ν_{max}(KBr)/cm^{-1} 1764 (CO); δ_H (optimized using LAOCOON III program) 1.750 (ddd, 1 H, –*J* 14.5, 13.00 and 6.50 Hz, CH$_2$), 2.428 (ddd, 1 H, –*J* 14.50, 2.50 and 0.50 Hz, CH$_2$), 2.575 (ddd, 1 H, *J* 13.00, 13.00 and 2.50 Hz, 4-H), 2.662 (ddddd, 1 H, *J* 12.00, 6.50, 1.30, 1.00 and 0.50 Hz, 3-H), 2.984 (dd, 1 H, *J* 12.0 and 4.50 Hz, 2-H), 3.123 (dd, 1 H, –*J* 13.85 and 4.29 Hz, SCH$_2$), 3.376 (ddd, 1 H, *J* 4.50, 4.29 and 2.50 Hz, 1-H), 3.391 (dd, 1 H, –*J* 13.85 and 2.50 Hz, SCH$_2$), 3.608 (ddd, 1 H, *J* 13.00, 1.30 and 1.00 Hz, 5-H), 6.806 (dd, 1 H, *J* 1.30 and 1.30 Hz, =CH) and 6.99–7.46 (m, 8 H, ArH).

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