Intramolecular Hetero Diels–Alder Reaction of 1-Thiabutadienes, 1-Aryl-3-[2-(alkenyloxy)phenyl]propene-1-thiones and 2-[2-(Alkenyloxy)benzylidene]-3,4-dihydronaphthalene-1(2*H*)-thiones

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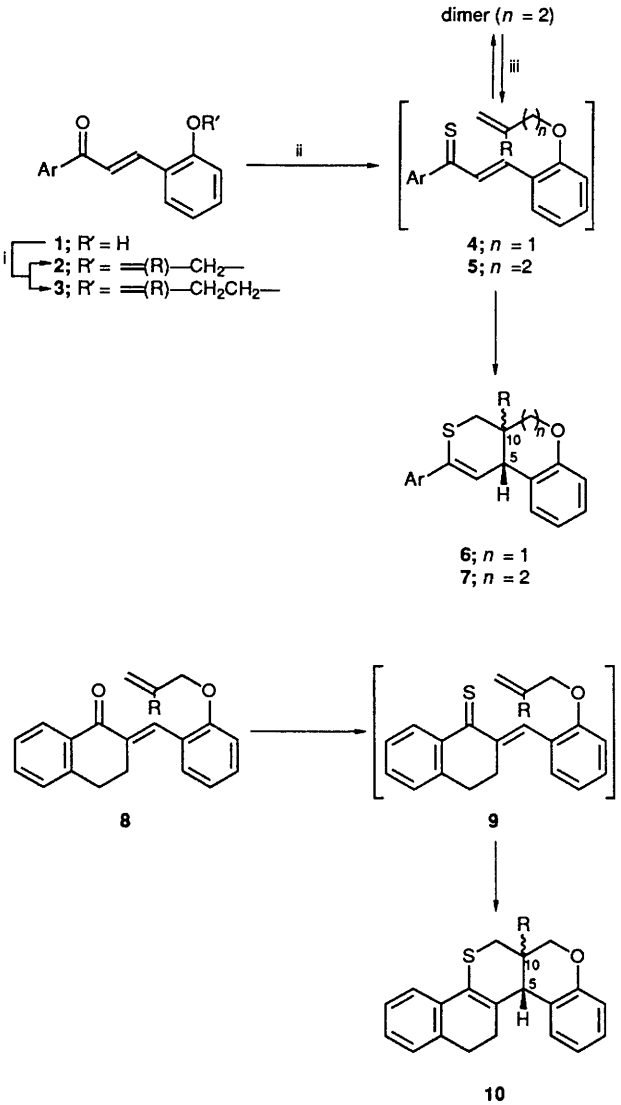
α,β-Unsaturated thioketones **4**, **5** and **9**, which are formed *in situ* by thionation of the corresonding ketones, undergo intramolecular hetero Diels–Alder reactions with high regio- and diastereo-selectivities (*trans/cis*) to give dihydrothiopyran-fused cycloadducts **6**, **7** and **10**.

Intramolecular Diels–Alder reactions provide useful methods for construction of polycyclic systems, and have been widely applied in organic synthesis.[1] Intramolecular hetero Diels–Alder (IHDA) reactions are also powerful synthetic procedures.[1,2] However, IHDA reactions involving a thiocarbonyl function have received little attention so far, examples being restricted to the internal trapping thioaldehyde intermediates by dienes.[3] We now report the first

Table 1 Thionation of ketones **2**, **3** and **8** and intramolecular hetero Diels–Alder reaction of thioketones **4**, **5** and **9**

Entry	Ketone	Ar	R	*n*	Solvent	Time/ h	Thio ketone	Product	Yield[a] (%)	Ratio[b] *trans : cis*
1	**2a**	Ph	H	1	C_6H_6	3	**4a**	**6a**	91	91 : 9
2	**2a**	Ph	H	1	CS_2	30	**4a**	**6a**	87	94 : 6
3	**2b**	*p*-MeC_6H_4	H	1	C_6H_6	3	**4b**	**6b**	91	91 : 9
4	**2c**	*p*-$MeOC_6H_4$	H	1	C_6H_6	2	**4c**	**6c**	87	90 : 10
5	**2d**	Ph	Me	1	C_6H_6	3	**4d**	**6d**	95	99 : 1
6	**3**	Ph	H	2	Toluene	1	**5**	**7**	58	45 : 55
7	**8a**	—	H	1	C_6H_6	2	**9a**	**10a**	88	22 : 78
8	**8b**	—	Me	1	C_6H_6	2	**9b**	**10b**	87	34 : 66

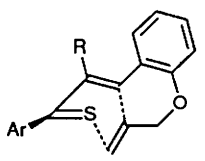
[a] Isolated yield of *trans* + *cis* isomers. [b] Determined by HPLC and ^1H NMR (500 MHz) spectroscopy.



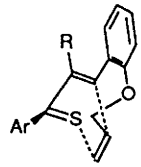
Scheme 1 *Reagents and conditions*: i, = (R)-$(CH_2)_n$-Br(Cl), K_2CO_3, KI, in refluxing acetone; ii, Lawesson's reagent or P_4S_{10}; iii, in refluxing toluene

example of IHDA reactions in which α,β-unsaturated thioketones participate as 4π-heterodiene partners.†

Thionation of the allyloxy chalcones **2a–c** with Lawesson's reagent in refluxing benzene (80 °C) [or with P_4S_{10} in refluxing carbon disulphide (Table 1, entry 2)] formed thiochalcones **4a–c**, which underwent the IHDA reaction immediately to give cycloadducts **6a–c**, skeletal thia-analogues of cannabinoids, in good yields with high regio- and diastereo-selectivities, the *trans*-fused isomers predominating (Table 1).‡ The reaction mixture became blue at the beginning of the reaction when **2a** was heated with P_4S_{10} in the presence of Et_3N at 46 °C



E-exo-anti



E-endo-syn

in carbon disulphide. The cycloadduct **6a** was finally obtained in 34% yield after heating for 10 h. This suggested the initial formation of the thioketone **4** which eventually afforded **6** *via* the IHDA process. In the reaction of **3** (n = 2) in refluxing benzene (80 °C), internal cyclization leading to the cycloadduct **7** was sufficiently slow to allow isolation of the thioketone dimer[5] instead of the monomeric **5**. On heating in toluene at 113 °C, the dimer regenerated **5** which was successfully trapped by the internal dienophile giving **7** as expected. The thionation and eventual IHDA reaction in one pot similarly gave **7** with lower stereoselectivity (entry 6). In contrast to the IHDA reactions of thiochalcones **4** (n = 1), thioketones **9** derived from α-tetralone produced cycloadducts **10** with preferential formation of the *cis*-isomers (entries 7 and 8). The structures of cycloadducts **6**, **7** and **10** were determined spectroscopically.§

These high diastereoselectivities can be explained by consideration of two possible, highly ordered transition states, *viz*, *E-exo-anti* and *E-endo-syn*[1] as the cycloadducts **6**, **7** and **10** are kinetically controlled products.¶ The reaction of **4** proceeds preferably *via* the *E-exo-anti* rather than the *E-endo-syn* transition state because an energetically unfavourable non-bonding interaction between the O–CH_2 part of the chain and the CH=CH of the diene destabilizes the *E-endo-syn* transition state. In contrast to the IHDA reaction of **4**, the *cis*-fused compounds **10** are the major products in the IHDA reaction of **9**. Molecular models show that in the *E-exo-anti* transition state there is strong steric interaction between the bridging CH_2CH_2 group and the proximal hydrogen of the tethering phenylene group in the chain. Accordingly the

† Recently the IHDA reaction of thiourea type compounds (1-thia-3-azadienes) has been reported.[4]

‡ The ketone **2**, **3** or **8** (1.0 mmol) was heated with Lawesson's reagent (1 mmol) in benzene or toluene (50 ml) under reflux for 1–3 h. Column chromatography [silica gel, ethyl acetate–hexane (1 : 10–15) as eluant] gave a mixture of *cis* and *trans* stereoisomers, which was then subjected to HPLC and spectral measurements. The major isomer was purified by preparative TLC and/or recrystallization.

§ The *cis* or *trans* configuration at the ring junction was deduced on the basis of ^{1}H NMR spectral data which showed characteristic coupling constants for such bicyclic systems.[6] In the *trans*-fused compounds, *e.g.* *trans*- **10a**, a large coupling constant, $J_{5,10}$ = 10.62 Hz, was observed, indicating a *trans*-diaxial relationship. That the 10-H occupies an axial position is also consistent with the observation that 10-H couples with the 1(ax)-H ($J_{1(ax),10}$ 10.62 Hz) in a *trans*-diaxial relationship and with the 1(eq)-H ($J_{1(eq),10}$ 4.03 Hz) in a synclinal axial–equatorial orientation. In the *cis*-fused compounds, a large coupling constant was not observed for 10-H (*e.g.* $J_{5,10}$ = 4.40, $J_{1,10}$ = 5.13 and 3.29 Hz in *cis*- **10a**. This is compatible with a conformation in which 10-H is equatorial and 5-H axial and hence the *cis* stereochemistry of these protons.

Spectroscopic data for **6a** (major, *trans*): ^{1}H NMR ($CDCl_3$; J values in Hz) δ 2.04–2.52 (m, 10-H), 2.78–2.86 (m, 9-H), 3.44 (dd, J 10.8, 2.5 Hz, 5-H), 3.74 (dd, J 10.8, 10.8, 1-H), 4.28 (dd, J 10.8, 4.0, 1-H), 6.31 (d, J 2.5, H-6) and 6.60–7.72 (m, 9H, Ar-H); ^{13}C NMR ($CDCl_3$) δ 28.78 (C-9), 33.87 (C-10), 38.11 (C-5), 69.89 (C-1) and 116.87–154.21; *m/z* 280 (100%, M^+); **10a** (*cis*): ^{1}H NMR δ 2.50–2.58 (m, 3H, 9,10-H), 2.80–3.02 (m, 4H, CH_2CH_2), 3.73 (d, J 4.40, 5-H), 4.26 (dd, J 10.99, 5.13, 1-H), 4.39 (dd, J 10.99, 3.29, 1-H) and 6.80–7.46 (m, 8H, Ar-H); ^{13}C NMR δ 26.17, 28.02 (CH_2CH_2), 31.24 (C-10), 31.39 (C-9), 40.35 (C-5), 68.92 (C-1) and 116.68–153.13; *m/z* 306(100, M^+).

¶ We assumed retention of the C=C *E*-configuration of the ketones (>98% by HPLC) during the thionation. The cycloadducts did not isomerize under the reaction conditions but decomposed to some extent after prolonged heating.

IHDA reaction of **9** proceeds *via* the *E-endo-syn* transition state in which the plane of the phenylene group is nearly perpendicular to that of the heterodiene to avoid steric congestion, thus causing the *cis* selectivity. These stereochemical demands in the transition states are valid as the dienophile approaches the heterodiene from a direction with tetrahedral angles of *ca.* 109° between the diene–dienophile plane and the developing bonds in the boat form.[7,8]

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