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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	on of thioketones 4, 5 and 9
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Entry	Ketone	Ar	R	n	Solvent	Time/ h	Thio ketone	Product	Yield ^a (%)	Ratio ^b trans : cis
1	2a	Ph	н	1	C ₆ H ₆	3	4 a	ба	91	91:9
2	2a	Ph	н	1	CŠ ₂	30	4 a	6a	87	94:6
3	2b	p-MeC ₆ H ₄	н	1	$C_6 \tilde{H}_6$	3	4b	6b	91	91:9
4	2c	p-MeOC ₆ H ₄	н	1	C ₆ H ₆	2	4c	6c	87	90:10
5	2d	Ph	Me	1	C_6H_6	3	4d	6d	95	99:1
6	3	Ph	Н	2	Toluene	1	5	7	58	45 : 55
7	8a		н	1	CeHe	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 Et₃N at 46 °C



in carbon disulphide. The cycloadduct 6a was finally obtained in 34% yield after heating for 10 h. This suggested the initial formation of the thicketone 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 dimer⁵ 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), thicketones 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–CH₂ 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 CH₂CH₂ group and the proximal hydrogen of the tethering phenylene group in the chain. Accordingly the

§ The *cis* or *trans* configuration at the ring junction was deduced on the basis of ¹H 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*): ¹H NMR (CDCl₃; *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); ¹³C NMR (CDCl₃) 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*): ¹H NMR δ 2.50–2.58 (m, 3H, 9,10-H), 2.80–3.02 (m, 4H, CH₂CH₂), 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); ¹³C NMR δ 26.17, 28.02 (CH₂CH₂), 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.

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

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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