Diene-transmissive hetero-Diels–Alder reaction of cross-conjugated azatrienes: a novel and efficient method for the synthesis of ring-fused nitrogen heterocycles

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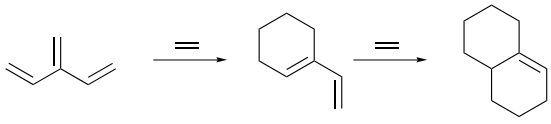
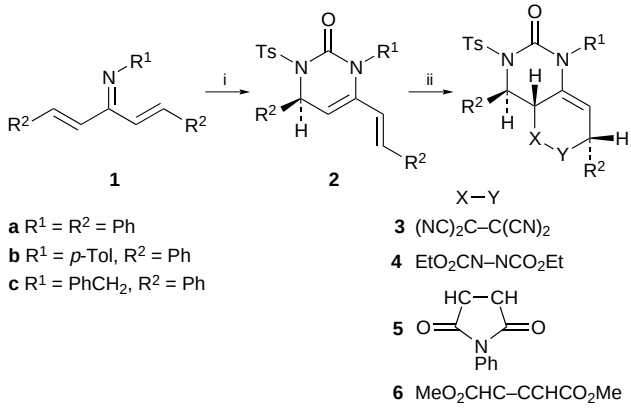
A diene-transmissive hetero-Diels–Alder reaction of cross-conjugated azatrienes, which provides a novel and efficient synthetic method for ring-fused, nitrogen-heterocyclic frameworks such as quinazolin-2-ones and pyrimido[5,4-*c*]-pyridazin-6-ones, is described for the first time.

The diene-transmissive Diels–Alder (DTDA) reaction is defined by two sequential (tandem) DA cycloadditions that involve an initial DA reaction of a cross-conjugated triene (or its equivalent) with a dienophile, followed by a second DA reaction of the mono-adduct on the newly-formed diene unit to give a bis-adduct (Scheme 1).[1] Tsuge *et al.* have developed the DTDA reactions.[2] However, the diene-transmissive hetero-Diels–Alder (DTHDA) reaction, in which one or more heteroatoms are contained within either a triene framework or a dienophile skeleton or both, has not been studied extensively, despite its high potential for construction of a wide range of ring-fused heterocycles; only a few reports have appeared so far.[3–6] In our previous reports, we disclosed the first examples of the DTHDA reactions in both inter- and intra-molecular modes of cycloadditions, in which divinyl thioketones were used as cross-conjugated heterotrienes.[3,4] Recently, Tsuge *et al.* reported the aza-DTHDA reaction of carbotrienes with strong diazo dienophiles such as azodicarboxylate and triazolinedione, and the oxa-DTHDA reaction of divinyl ketones with an enamine (initial cycloaddition) followed by tetracyanoethylene or triazolinedione (second cycloaddition).[5] Spino and Liu showed that cyclic 2-formyl 1,3-dienes also took part in the oxa-DTHDA reaction for the construction of a quassinoid framework.[6] Although azabutadienes constitute a class of widely investigated heterodienes in HDA cycloaddition reactions,[7] there are no reports on the aza-DTHDA cycloaddition of cross-conjugated azatrienes capable of 4π participation. We report here for the first time on the aza-DTHDA reaction of such azatrienes. The methodology constitutes a new facile access to a variety of functionalized, ring-fused nitrogen heterocycles with high efficiency and predictable stereoselectivity.

When the di-β-styrylmethanimine **1**† (16 mmol) was allowed to react with tosyl isocyanate (2–3 equiv.) at room temp. in xylene (15 cm^3) for 0.5–1 h, the 1 : 1 cycloadduct **2**‡ was obtained in good yield (Scheme 2, Table 1). Neither the regioisomer nor the bis-adduct were detected in the reaction mixture. A second DA cycloaddition of the diene **2** with tetracyanoethylene (TCNE) proceeded smoothly at room temp. to give a quantitative yield of the cycloadduct **3**‡ with complete stereoselectivity. The stereochemistry of the cycloadduct **3** was deduced from its ^{1}H NMR spectrum based mainly on the coupling constants, for example for **3a** $^3J_{4,4a}$ 5.0, $^4J_{4a,7}$ 2.3, $^4J_{4a,8}$ 2.3 and $^3J_{7,8}$ 3.6 Hz, suggesting that, in the second cycloaddition, the dienophile cycloadds from the less hindered bottom side (*anti* to R^2) of **2** in which the substituent R^2 at C-4 occupies an axial arrangement in accord with the observed coupling constant $J_{4,5}$ (*e.g.* 6.9 Hz for **2a**). Dimethyl azodicarboxylate (DAD) also afforded highly stereoselectively the



Scheme 1



Scheme 2 *Reagents and conditions*: i, TsNCO, xylene, room temp., 0.5–1 h; ii, X=Y, solvent, room temp. or heat

Table 1 Initial cycloaddition of **1** to afford mono-cycloadducts **2**

Azatriene	Reaction time/h	Cycloadduct (% yield)[a]
1a	1	**2a** (90)
1b	0.5	**2b** (91)
1c	0.5	**2c** (93)

[a] Isolated yield in a one-pot reaction from the divinyl ketones *via* method A.†

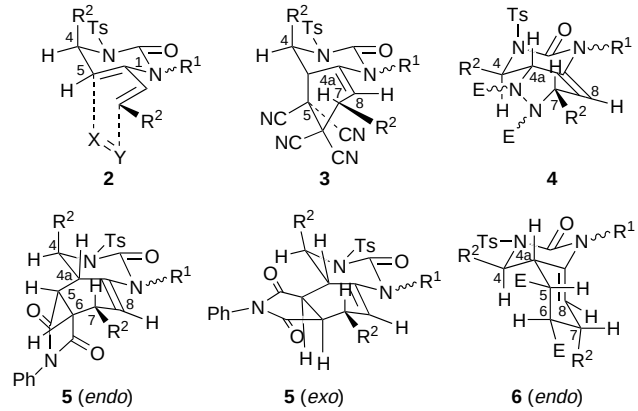


Fig. 1

Table 2 Second cycloaddition of **2** to afford bis-cycloadducts **3**–**6**

Run	Dienophile[a]	Diene	Reaction conditions	Cycloadduct (% yield)[b]	Ratio[c]
1	TCNE	**2a**	Benzene, room temp., 5 min	**3a** (99)	—
2		**2b**	Benzene, room temp., 5 min	**3b** (97)	—
3		**2c**	Benzene, room temp., 5 min	**3c** (99)	—
4	DAD	**2a**	Toluene, 110 °C, 10 min	**4a** (94)	—
5		**2b**	Toluene, 110 °C, 10 min	**4b** (89)	—
6		**2c**	Toluene, 110 °C, 10 min	**4c** (99)	—
7	NPMI	**2a**	Toluene, 110 °C, 7 h	**5a** (97)	56 : 44
8		**2b**	Toluene, 110 °C, 17 h	**5b** (88)	70 : 30
9		**2c**	Toluene, 110 °C, 4 h	**5c** (99)	38 : 62
10	DMF	**2a**	Toluene, 110 °C, 9 h	**6a** (99)	57 : 43
11		**2b**	Toluene, 110 °C, 17 h	**6b** (91)	59 : 41
12		**2c**	Toluene, 110 °C, 9 h	**6c** (99)	53 : 47

[a] TCNE: tetracyanoethylene; DAD: diethyl azodicarboxylate; NPMI: *N*-phenylmaleimide; DMF: dimethyl fumarate. [b] Isolated yield. [c] Ratio (*endo* : *exo*) determined by ^{1}H NMR spectroscopy. The term *endo* refers to a *cis*-relationship between H_{4a} and H_5 and the term *exo* a *trans*-relationship.

cycloadduct **4**‡ in good yield. With *N*-phenylmaleimide (NPMI) and dimethyl fumarate (DMF) second cycloadditions were effected upon heating in toluene for 4–17 h to produce excellent yields of the cycloadducts **5** and **6** with complete diastereoisoface selectivity but with almost no *endo* : *exo*-selectivity. The results are summarised in Table 2. Fig. 1 shows the most probable stereochemical (conformational and configurational) structures of the mono- (**2**) and bis-cycloadducts (**3**–**6**) which were deduced from ^{1}H NMR spectroscopic studies and computational calculations using MOPAC 93, CONFLEX, LAOCOON III and 3JHH2 programs.[4,10,11]

Thus, it has been shown that the DTHDA methodology of cross-conjugated azatrienes is successfully applied to a synthesis of ring-fused nitrogen heterocycles.

Footnotes

† The imine **1** was prepared by Barluenga's method involving the reaction of iminophosphorane with prop-2-ynyltriphenylphosphonium salt, followed by successive treatment with an aldehyde, butyllithium and an aldehyde (Method B, 60–70% yield).[8] Otherwise, the imine **1** was more conveniently prepared by the condensation reaction of di-β-styryl ketone with an amine in the presence of $TiCl_4$ and triethylamine (method A, 90–95% yield).[9]

‡ *Selected data* for **2a**: mp 132–133 °C; *m/z* 506 (M^+, 0.5%) and 309 (M^+ − TsNCO, 100%); ν_{max} (KBr)/cm^{-1} 1170, 1362 (SO_2) and 1698 (CO); δ_H (270 MHz, $CDCl_3$) 2.19 [s, 3 H, CH_3 (Ts)], 5.73 (d, 1 H, *J* 6.9 Hz, 5-H), 5.85 (d, 1 H, *J* 16.2 Hz, 7-H), 6.09 (d, 1 H, *J* 6.9 Hz, 4-H), 6.57 (d, 1 H, *J* 16.2 Hz, 8-H), 6.90 (d, 2 H, *J* 8.58 Hz, ArH), 6.97–7.02 (m, 2 H, ArH) and 7.08–7.31 (m, 15 H, ArH); δ_C (DEPT, $CDCl_3$) 21.5 (CH_3), 56.9 (CH), 103.8 (CH, C-5), 120.5 (CH), 125.6 (2CH), 125.8 (2CH), 127.0 (CH), 127.4 (CH), 127.5 (CH), 127.6 (2CH), 127.7 (2CH), 127.8 (2CH), 128.0 (2CH), 128.06 (2CH), 128.10 (2CH), 131.3 (CH), 135.8 (C), 136.0 (C), 137.1 (C), 137.5 (C), 140.3 (C), 140.0 (C) and 150.0 (CO). For **3a**: mp 160–163 °C; *m/z* (FAB) 635 (M^+ + 1, 2%), 309 (M^+ − TCNE − TsNCO, 98%) and 308 (100%); HRMS (FAB) found M^+ + 1 635.1860 $C_{37}H_{27}O_3N_6S$ requires M + 1, 635.1868; ν_{max} (KBr)/cm^{-1} 1174, 1364, 1718 (CO) and 2256 (CN); δ_H (270 MHz, $CDCl_3$, [H,H]-COSY) 2.31 [s, 3 H, CH_3 (Ts)], 3.92 (dd, 1 H, *J* 5.0, 2.3 and 2.3 Hz, 4a-H), 4.32 (dd, 1 H, *J* 3.6 and 2.3 Hz, 7-H), 5.29 (dd, 1 H, *J* 3.6 and 2.3 Hz, 8-H), 6.14 (d, 1 H, *J* 5.0 Hz, 4-H), 6.99 (d, 2 H, *J* 8.6 Hz, ArH) and 7.29–7.48 (m, 17 H, ArH); δ_C (DEPT, $CDCl_3$) 21.5 (CH_3), 42.7 (C), 45.5 (C), 47.7 (CH), 49.1 (CH), 59.4 (CH), 108.0 (CN), 109.1 (CN), 110.3 (CN), 111.2 (CN), 111.7 (CH), 127.4 (2CH), 128.0 (2CH), 128.8 (2CH), 129.1 (CH), 129.3 (4CH), 129.76 (2CH), 129.81 (CH), 130.1 (2CH), 130.3 (2CH), 130.6 (CH), 131.0 (C), 135.0 (C), 135.4 (C), 137.1 (C), 137.2 (C), 144.9 (C) and 149.4 (CO). For **5a** (*exo*): mp 151–152 °C; *m/z* 679 (M^+ + 1, 24%), 525 (M^+ − TsH, 32%) and 481 (100%); ν_{max} (KBr)/cm^{-1} 1170, 1386 and 1716 (CO); δ_H (270 MHz, $[^2H]_{10}$- *p*-xylene, [H,H]- and [C,H]-COSY in $CDCl_3$) 1.86 [s, 3 H, CH_3 (Ts)], 2.21 (dd, 1 H, *J* 10.6 and 10.6 Hz, 5-H), 2.66 (br d, 1 H, *J* 10.6 Hz, 4a-H), 3.13 (br d, 1 H, *J* 10.6 Hz, 7-H), 3.34 (dd, 1 H, *J* 10.6 and 10.6 Hz, 6-H), 4.83 (br s, 1 H, 8-H), 6.90 (br s, 1 H, 4-H) and 6.58–7.82 (m, 24 H, ArH); δ_C (DEPT, $CDCl_3$) 21.5 (CH_3), 43.2 (CH), 43.6 (CH), 46.1 (CH), 48.2 (CH), 58.7 (CH), 115.8 (CH), 126.1 (2CH), 126.3 (2CH), 127.4 (CH), 127.8 (CH), 128.3 (2CH), 128.5 (2CH), 128.68 (CH), 128.75 (2CH), 128.9 (3CH), 129.1 (6CH), 129.6 (CH), 131.3 (C), 135.4 (C), 137.0 (C), 139.3 (C), 139.4 (C), 141.5 (C), 144.4 (C), 150.7 (CO), 174.7 (CO) and 176.7 (CO).

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