Tandem Conjugate Carbon Addition–Intermolecular Hetero Diels–Alder Reactions using Ethyl 1*H*-Perimidine-2-acetate as a Ketene Aminal with Heating or Microwave Activation†

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The reaction of ethyl 1*H*-perimidine-2-acetate **3** as a heterocyclic ketene-aminal with 2.1 equiv. of ethyl propiolate **4a** or but-3-yn-2-one **4b** affords new fused perimidines in good yields by a tandem C-addition/hetero Diels–Alder reaction; the new 1-azabuta-1,3-diene intermediates are generated *in situ* from the initial *trans* C-addition products by thermal 1,5-prototropy.

The hetero Diels–Alder reaction involving heterodienophiles[1] and/or heterodienes[2] has become a powerful tool for the construction of heterocyclic rings, particularly in natural product synthesis.[3]

1 R = R′CO, $PhSO_2$, Me_2N, Ph **2** EWG = CO_2Et, CN X = O, S

Scheme 1

However, the Diels–Alder reactions of 1-azabuta-1,3-dienes of simple α,β-unsaturated imines **1** suffer from low conversion, and/or imine tautomerization precluding [4 + 2] cycloaddition.[2a] To solve these problems, various 1-azabuta-1,3-dienes carrying substituents at the 1-position (R = acyl,[3] sulfonyl,[4] dimethylamino,[5] phenyl[6]) have been developed to avoid instability arising from the imine moiety.

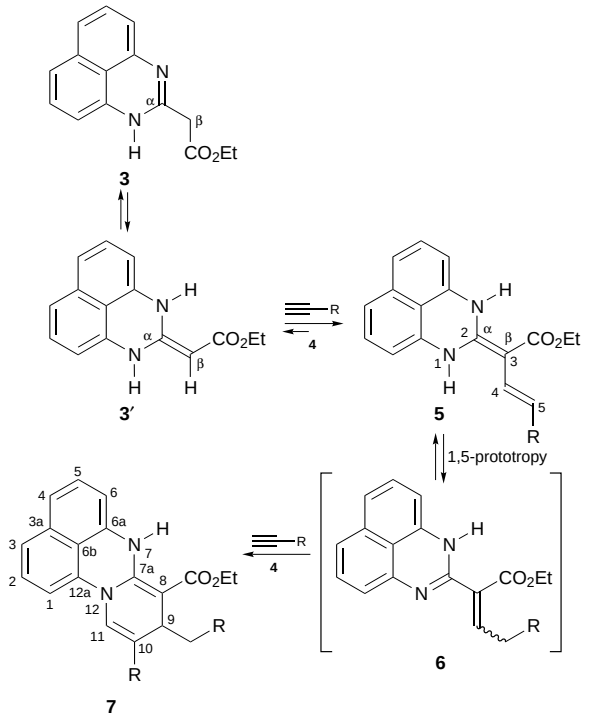
Recently, Sakamoto *et al.*[7] reported an interesting type of 1-azabuta-1,3-diene **2** (Scheme 1) in which the imine moiety is stabilized when introduced in a heterocyclic ring, such as 1,3-benzoxazoles and 1,3-benzothiazoles. The dienes **2** react with both electron-deficient and electron-rich dienophiles in intermolecular [4 + 2] cycloadditions.

A recurrent theme of our ongoing studies with ethyl 1*H*-perimidine-2-acetate **3** (Scheme 2) is the nucleophilic reactivity of the β-position. Perimidine **3** simultaneously exhibits the distinct properties of heteroatomic systems with an excess of and a deficiency of π-electrons.[8] Owing to the conjugation effect of the electron-donating amino groups and electron-withdrawing substituents, the double bond $C_\alpha{=}C_\beta$ is highly polarized and the electron density on C_β is increased,[9] leading to greater nucleophilicity of carbon when compared to nigrogen.[10] Encouraged by using perimidine **3** as an N,C bisnucleophilic synthon towards annulation from α- and β-dielectrophiles,[11] we report here the first results obtained for the synthesis of new fused perimidines by a tandem conjugate C-addition–hetero Diels–Alder reaction. Moreover, as part of our programme to develop organic syntheses under microwave irradiation,[12] we extended these reactions using solvent-free conditions under focused microwaves.[13a]

Results and Discussion

Treatment of **3** with 1.1 equiv. of ethyl propiolate **4a** (MeOH, reflux, 3 h) mainly afforded the insoluble *trans* C-addition product **5a**[14] (Scheme 2, Table 1). Further treatment of **3** with 2.1 equiv. of **4a** in refluxing ethanol for 3 h led to the fused perimidine **7a** in quantitative yield (Table 1). The assigned structures of **5a** and **7a** were substantiated by the ^1H and ^{13}C NMR and MS analyses. Starting from **5a** and **4a** (**5a:4a** = 1:1) under the same reaction conditions (EtOH, reflux, 3 h), compound **7a** was also obtained in 98% crude yield: we reasoned that, by reacting the initial C-addition product **5a** with **4a**, the tautomer **6a** might be readily trapped by an aza-Diels–Alder cycloaddition with the dienophile **4a**.

Interestingly, when **5a** was refluxed in EtOH for 3 h, the ^1H NMR spectrum of the crude reaction mixture showed the presence of compounds **3** (50%) and **7a** (50%) as a result of a retro-reaction to give **3** and **4a**, the latter reacting with the remaining **5a** to give **7a**. Finally, when an equimolecular mixture of **5a** and *N*-phenyl- or *N*-methyl-maleimide as dienophile were refluxed in ethanol for 12 h, no Diels–Alder reaction took place but the labile nature of the vinylene segment of C_β in **5a** was observed by identification of compounds **7a**



3 **3′** **5** **6** **7**

4a,5a,7a R = CO_2Et **4b,5b,7b** R = COMe

Scheme 2

Table 1 Synthesis of perimidines **5a** and **7a–b** from **3** and **4a–b**

Product	R	Reaction conditions	**4:3**	Yield (%)
5a	CO_2Et	MeOH, 65 °C, 3 h	1.1:1	67[a]
7a	CO_2Et	EtOH, 78 °C, 3 h	2.1:1	98 78[b]
7b	COMe	EtOH, 78 °C, 5 h	2.1:1	98 50[b]

[a]Yield of crude **5a** obtained after filtration on a Buchner funnel. [b]Yield of crude product estimated by ^1H NMR and after chromatography on silica gel.

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Table 2 Synthesis of **7a** using an oil bath or under focused microwave irradiation ($\mu\omega$)

Entry	t/min	Reaction conditions	Yield (%)[a]		
			3	**5a**	**7a**
1[d]	8	$\mu\omega$[b]	≤2	0	98
2	8	oil bath[c]	≤2	0	98
3[e]	35	$\mu\omega$	≤2	0	98
4[e]	35	oil bath	≤2	0	98
5[e]	40	EtOH/$\mu\omega$	38	38	24
6[e]	40	EtOH/oil bath	38	38	24

[a]Yield of crude product estimated by ^{1}H NMR. [b]Reactions were run in a focused microwave oven (Synthewave 402®). [c]In a thermostatted oil bath, temperature variation ±1 °C. [d]110 °C. [e]78 °C.

and **3** (**7a:3** = 1:1): the formation of **7a** can be explained *via* a retro-addition reaction from **5a** in ethanol (Scheme 2).

Mechanistically, the reaction proceeds *via* the initial formation of the *trans* compound **5a** by regioselective C_β-addition of ethyl propiolate **4a** to perimidine **3** which affords the 1-azabuta-1,3-diene **6a** *in situ*, by thermal 1,5-prototropy, then **6a** reacts with a second equivalent of **4a** as dienophile and gives **7a** by [4 + 2] cycloaddition.

In a further demonstration of this methodology, treatment of **3** with but-3-yn-2-one **4b** (EtOH, reflux, 5 h) afforded **7b** together with a small amount of **5b** (Scheme 2). Purification on silica gel (CH_2Cl_2–MeCN, 19:1 as eluent, R_f 0.36) gave pure **7b** in 50% yield (Table 1).

In order to shorten the synthetic route to **7a**, solvent-free conditions in an oil bath or focused microwave irradiation were used.[13a] A Synthewave 402® microwave oven monitored by a computer which adjusts the temperature[13b] of the reaction mixture was used. Some typical examples are shown in Table 2. The main features of this technique are, complete addition in less than 8 minutes and ease of purification of **7a**. When the same reaction mixture was heated in an oil bath previously set at the same boiling point for the same reaction time (entries 3,4 and 5,6) the results were analogous. In these cases, a specific microwave effect can be excluded as it is not expected in this polar solvent,[15] but microwave heating affords a straightforward and efficient method for the preparation of **7a**.

Experimental

General Procedure for the Preparation of Fused Perimidines **7**.—A mixture of ethyl 1*H*-perimidine-2-acetate **3** (1 g, 3.9 mmol) and **4** (8.2 mmol) in dry ethanol (20 ml) was heated at 78 °C for 3 h under vigorous magnetic stirring. After elimination of ethanol *in vacuo*, the crude residue was purified by chromatography on silica gel. Solvent evaporation gave the desired compound **7** as a nearly pure oil which crystallized on standing.

Diethyl 9-ethoxycarbonylmethyl-7,9-dihydropyrido[1,2-a]*perimidine-8,10-dicarboxylate* **7a** was prepared from ethyl propiolate **4a** (0.8 g, 8.2 mmol) as a colourless powder, mp = 144–146 °C (from CH_2Cl_2–MeCN, 19:1 as eluent, R_f 0.79), 78% yield; δ_H ($CDCl_3$, 300 MHz) 1.00 (t, 3 H, *J* 7.1 Hz), 1.38 (t, 2 × 3 H, *J* 7.1 Hz), 2.61 (d, 2 H, *J* 5.7 Hz), 3.55 (qd, 2 H, *J* 7.1 Hz), 4.25 (2 × q, 2 × 2 H, *J* 7.1 Hz), 5.68 (t, 1 H, *J* 5.7 Hz), 6.52 (d, 1 H, H-4), 6.89 (d, 1 H, H-9), 7.21 (m, 4 H, Ar), 7.81 (s, 1 H, =CH), 12.21 (br s, 1 H, NH); δ_C ($CDCl_3$, 75 MHz) 13.7 (qt, *J* 127, 2.7 Hz), 14.5 (qt, *J* 127, 2.5 Hz), 14.6 (qt, *J* 127, 2.5 Hz), 37.3 (td, *J* 132, 2.1 Hz), 50.5 (dt, *J* 147 Hz, CH), 60.0 (tq, *J* 147, 4.4 Hz), 60.2 (tq, *J* 147. 4.4 Hz), 60.9 (tq, *J* 147, 4.4 Hz), 81.8 (s, C-8), 105.5–106.1 (dd, *J* 161 Hz, C-1, C-6), 105.7 (s, C-10), 117.8 (s, C-6b), 119.9–121.1 (d, *J* 160 Hz, C-3, C-4), 127.8 (d, *J* 160 Hz, C-2, C-5), 131.8–134.3 (sd, C-6a, C-12a), 134.6 (s, C-3a), 135.2 (dd, *J* 166, 4.2 Hz, C-11), 150.2 (s, C-7a), 165.2 (sm, CO), 168.3 (sm, OC), 170.1 (sm, CO) (Found: *m*/*z*, 450.1775. $C_{25}H_{26}N_2O_6$ requires M_r 450.1790).

Ethyl 10-acetyl-9-(2-oxopropyl)-7,9-dihydropyrido[1,2-a]*perimidine-8-carboxylate* **7b** was prepared from but-3-yn-2-one **3b** (0.56 g, 8.2 mmol) as a colourless powder, mp = 182–184 °C (from CH_2Cl_2–MeCN, 19:1 as eluent, R_f 0.36), 50% yield; δ_H ($CDCl_3$, 300 MHz) 1.39 (t, 3 H, *J* 7 Hz), 2.16 (s, 3 H), 2.34 (s, 3 H), 2.72 (2 × d, 2 H), 4.28–4.29 (2 × q, 2 H, *J* 7 Hz), 5.88 (2 × d, 1 H, *J* 7 Hz), 6.59 (dd, 1 H, *J* 7, 1.5 Hz), 7.05 (d, 1 H, *J* 7 Hz), 7.22 (s, 1 H, H-4), 7.22 (m, 4 H, Ar), 7.78 (s, 1 H, =CH), 12.32 (br s, 1 H, NH); δ_C ($CDCl_3$, 75 MHz) 14.6 (qt, *J* 127, 2.5 Hz), 24.1–31.2 (2 × q, *J* 127 Hz), 45.5 (tm, *J* 130 Hz), 49.3 (dq, *J* 147 Hz), 60.3 (tq, J 147, 4.5 Hz), 82.2 (sd, *J* 2.7 Hz, C-8), 105.6 (dm, *J* 160 Hz, C-6), 106.4 (dd, *J* 160 Hz, C-1), 116.3 (sm, C-6b), 118.0 (sq, C-10), 120.3–121.4 (dm, *J* 160 Hz, C-3, C-4), 127.9–128.0 (d, *J* 160 Hz, C-2, C-5), 131.6–134.7 (sd, C-6a, C-12a), 134.7 (sm, C-3a), 136.9 (dd, *J* 162, 3.8 Hz, C-11), 150.2 (st, C-7a), 168.1 (sm, CO), 193.4 (sm, CO), 205.4 (sm, CO) (Found: *m*/*z*, 390.1552. $C_{23}H_{22}N_2O_4$ requires M_r, 390.1580).

Ethyl 4-(2,3-Dihydro-1H-perimidin-2-ylidene)-4-ethoxycarbonylbut-2-enoate **5a**.—Ethyl 1*H*-perimidine-2-acetate **3** (1 g, 3.9 mmol) and ethyl propiolate **4a** (0.42 g, 4.3 mmol) were added to dry methanol (10 ml) and the mixture refluxed at 65 °C for 3 h with vigorous magnetic stirring. The methanol was removed *in vacuo* and the crude reaction mixture was triturated with dry diethyl ether (20 ml). After standing (1 h), the precipitated product was filtered off, washed with diethyl ether (2 × 10 ml) and dried in a dessicator over $CaCl_2$ to afford compound **5a** (0.94 g, 67%); δ_H ([$^2H_6$]DMSO, 300 MHz) δ 1.26 (2 × t, 6 H, *J* 7 Hz), 4.14 (2 × q, 4 H, *J* 7 Hz), 6.12 (d, 1 H, =CH, *J* 15 Hz), 6.76 (m, 2 H, H-4, H-9), 7.15 (m, 4 H, Ar), 7.70 (d, 1 H, =CH, *J* 15 Hz), 11.40 (br s, 2 H, NH); δ_C ([$^2H_6$]DMSO, 75 MHz) 14.2 (qt, *J* 127, 2.5 Hz), 14.4 (qt, *J* 127, 2.5 Hz), 58.6 (tq, *J* 148, 4.8 Hz), 59.4 (tq, *J* 148, 4.8 Hz), 79.7 (s, C_β), 106.1 (dm, *J* 163 Hz, =CH), 108.0 (dd, *J* 166, 5.1 Hz, C-4, C-9), 115.6 (sm, C-9b), 119.1 (dm, *J* 160 Hz, C-5, C-8), 127.9 (d, *J* 159 Hz, C-6, C-7), 133.5–133.6 (s, C-3a, C-9a, C-6a), 137.5 (d, *J* 148 Hz, =CH), 152.4 (s, C-2), 168.5 (sd, CO), 169.5 (sd, *J* 9 Hz, =CH—CO) (Found: *m*/*z*, 352.1432. $C_{20}H_{20}N_2O_4$ requires M_r 352.1423).

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