SHORT PAPER

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Competitive azomethine ylide cycloaddition and carbonyl-ene reaction in the treatment of 4-(alk-2-enyl)amino-2-formylpyr-2(2*H*)-ones with sarcosine ethyl ester†

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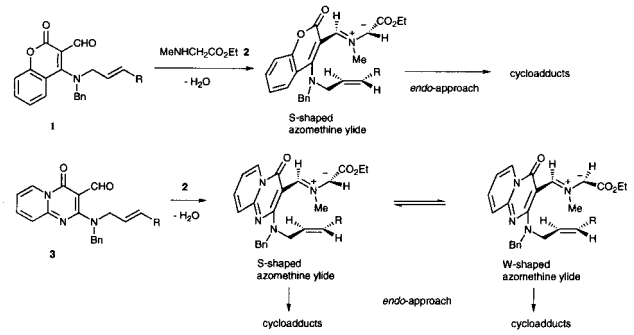
The thermal reaction of 4-(alk-2-enyl)amino-2-formyl-2)2*H*)-pyrones **4** with sarcosine ethyl ester (**2**) gave two isomeric pyrrol[3,4-*c*]pyrano[4,3-*d*]pyridines **5** and **6**, arising from the *endo*-cycloaddition of the resulting S- and W- shaped azomethine ylides, and [1,3]oxazines **8** *via* the carbonyl-ene reaction of pyrones **4** depending on the reaction conditions.

In a previous paper,[1] we reported that the reaction of 4-(alk-2-enyl)benzylamino-3-formylchromen-2(*2H*)-ones **1** with sarcosine ethyl ester (**2**) in benzene at reflux gave azomethine ylide intermediates, which underwent an intramolecular cycloaddition leading to chromeno[4,3-*b*]-pyrrolo-[2,3-*d*]pyridin-11(11*H*)-ones as single isomers *via* an *endo*-approach of the S-shaped azomethine ylides. More recently,[2] we also reported that the reaction of 2-(alk-2-enyl)benzyl-amino-3-formylpyrido[1,2-*a*]pyrimidin-4(4H)-ones **3** with **2** gave two isomeric azomethine ylide-cycloadducts *via* an *endo*-approach of the S- and W- shaped azomethine ylides (Scheme 1).



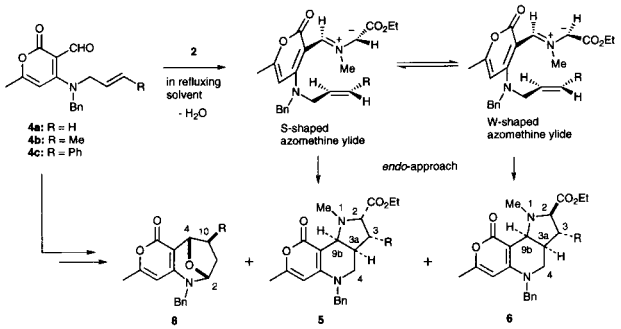
Scheme 1

While the dipole generated from aldehyde **3** and sarcosine ethyl ester (**2**) existed as a mixture of S- and W- forms, the dipole from aldehyde **1**, which deemed more hindered than the former, did as an S-form. We, therein, proposed that the equilibrium between S- and W-shaped azomethine ylides was controlled not by the electronic nature of the dipoles induced by heterocyclic systems but by the steric hindrance around the dipole and dipolarophile. To check this working model, we examined the reaction of the azomethine ylide from 4-(alk-2-enyl)benzylamino-2-formylpyr-2(2*H*)-ones **4** and **2**, which is less hindered than that from aldehyde **1** and **2**.

The reaction 4-(*N*-allylbenzylamino) substrate **4a** with **2**, in toluene at reflux for 24 h gave two isomeric azomethine ylide-cycloadducts **5a** and **6a** (58%; as a 1:1 mixture) together with **8a** (13%). The structure of **5a** and **6a** were easily assigned on the basis of their elemental analyses and spectroscopic data in comparison with those of the corresponding cycloadducts in the reaction of **3.**[2,3] Based on their structural assignment, the formation of **5a** was ascribed to the *endo*-approach of the S-shaped azomethine ylide, while that of **6a** was ascribed to the *endo*-approach of the W-shaped one. On the other hand, the structure of **8a** was deduced to be 1-benzyl-7-methyl-1,2-dihydro-2,4-ethanopyrrolo[4,3-*d*][1,3]oxazin-5(*4H*,*5H*)-one, which was regarded as a secondary product from 1-benzyl-5-hydroxy-8-methyl-4,5-dihydropyrrolo[4,3-*b*]azepin-6(*1H*)-one (**7a**), a carbonyl ene product of **4a.** Similar carbonyl ene reaction was also observed in the thermal reaction of aldehyde **1.**[1]

The reaction utilizing *N*-(*E*)-but-2-enyl substrate **4b** and *N*-(*E*)-cinnamyl one **4c** also gave **5b, c** and **6b, c** in moderate total yields together with [1,3]oxazines **8b, c** (Scheme 2 and Table 1). The configuration of the 10-H of [1,3]oxazines **8b, c** was deduced to be *endo* from the coupling constants between the 4- and 10- H ($J_{4,10}$ = *ca* 0 Hz).

These findings were consistent with the proposed equilibrium between the S- and W- shaped azomethine ylides controlled by the steric hindrance. The carbonyl ene reaction of **4** was competitive with the azomethine ylide formation from **4** at an elevated reaction temperature.



Scheme 1

Table 1 Reaction of aldehydes **4** with sarcosine ethyl ester (**2**)

Run	Aldehyde	Reaction conditions	Products (yield %)[a]
1	**4a**	Benzene, 80 h	**5a** (22) **6a** (16)
2	**4a**	Toluene, 24 h	**5a** (29) **6a** (29) **8a** (13)
3	**4b**	Benzene, 80 h	**5b** (49) **6b** (23) **8b** (trace)
4	**4b**	Toluene, 24 h	**5b** (34) **6a** (22) **8b** (20)
5	**4c**	Toluene, 26 h	**5c** (48) **6c** (trace) **8c** (34)

[a]Based on isolated products.

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† This is a Short Paper, there is therefore no corresponding material in *J Chem. Research (M).*

Table 2 Thermal ene reaction of aldehydes **4**

Run	Aldehyde	Reaction conditions	Products (yield %) [a]
1	**4a**	Toluene, 48 h	**8a** (60) **9a** (21)
2	**4a**	Xylene, 12 h	**8a** (44) **9a** (34)
3	**4b**	Xylene, 20 h	**7b** (13) **8b** (42) **9b** (14)
4	**4c**	Xylene, 20 h	**8c** (86) **9c** (7)

[a] Based on isolated products.

Our next concern was focused on the thermal behaviours of aldehydes **4;** heating **4a** in toluene at reflux for 48 h gave [1,3]oxazine **8a** and azepine **9a** in 60 and 21% yield, respectively. Compound **9a** was obtained as characteristic brown crystals and its formation was ascribed to dehydration of the initially formed azepine **7a**. the reaction of **4b** in toluene at reflux gave **7b, 8b** and **9b.** The structure of azepine **7b**, a primary product in ene reaction of this system, was also assigned on the basis of the elemental analysis and spectroscopic data in comparison with those of the ene products previously reported.[1,4] The stereochemistry between the 4- and 5-position of the azepine ring of **7b** was deduced to be *cis* from the coupling constant ($J_{4,5}$ = ca. 0 Hz).[4] Acid treatment of azepine **7b** gave the desired [1,3]oxazine **8b** in a good yield. Similar ene reaction of **4c** in xylene at reflux gave **8c** and **9c** in a good total yield. Thermal reaction of aldehydes **4** performed a carbonyl ene reaction to afford azepines **7** stereoselectively, which were converted into [1,3]oxazines **8** and fully conjugated azepines **9** during the reaction.

Experimental

The usual instruments general procedures and chromatographic procedures are given in ref. 3.

Reaction of aldehyde **4b** *with sarcosine ethyl ester (***2***); General procedures:* a solution of aldehyde **4b** (0.15 g, 0.5 mmol), sarcosine ethyl ester hydrochloride (0.1 g, 0.65 mmol), and diisopropylethylamine (0.17 ml, 0.95 mmol) in toluene (10 ml) was heated under reflux for 24 h. the resultant precipitates were filtered off and the filtrate was evaporated to dryness. The residue was subjected to column chromatography on silica gel to afford **6b** and **5b** as elution of hexane/ethyl acetate (2/1) and **8b** (hexane/ethyl acetate = 1/1).

(*2S**,3*aR**,9*bS**)-(±)-5-Benzyl-2-(ethoxycarbonyl)-1,3,7-trimethyl-2,3,3a,4,5,9b-hexahydropyrrolo[3,4-*c*]pyrano[4,3-*d*]pyridin-9(1*H*)-one (**5b**): pale yellow prisms from hexane-benzene; m.p. 184–186ºC (Found: C, 69.55; H, 7.39; N, 6.78. $C_{23}H_{38}N_2O_4$ requires C, 69.67; H, 7.12; N, 7.07); – (KBr): 1725, 1680 cm^{-1} (CO); δ_H ($CDCl_3$): 0.97 (3H, d, *J* 7.3, 3-Me), 1.29 (3 H, t, *J* 7.3, CH_2*Me*), 2.03 (1 H, m, 3a-H), 2.13, 2.56 (each 3 H, each s, 1- and 7-Me), 2.26 (1 H, m, 3-H), 3.10-3.13 (2 H, m, 4-H), 3.82 (1 H, d, *J* 8.3, 2- H), 4.21 (2 H, q, *J* 7.3, *CH*$_2$*Me*), 4.45 (1 H, d, *J* 6.6, 9b- H), 4.52 (2 H, br, s, C*H*$_2$Ph), 5.78 (1 H, s, 6-H), 7.15-5.40 (5 H, Ph); δ_C ($CDCl_3$): 14.6, 15.1, 20.4, 36.4, 37.8, 42.6, 50.1, 54.4, 54.6, 60.0, 69.5, 92.6, 95.5, 126.9, 127.8, 129.1, 136.3, 155.3, 160.6, 164.8, 172.1.

(*2R**,3*aR**,9*bS**)-(±)-5-Benzyl-2-(ethoxycarbonyl)-1,3,7-trimethyl-2,3,3a,4,5,9b-hexahydropyrrolo[3,4-*c*]pyrano[4,3-*d*]pyridin-9(1*H*)-one (**6b**): pale yellow needles from hexane–benzene; m.p. 178–181°C (Found: C, 69.39; H, 7.04; N, 6.94. requires C, 69.67; H, 7.12; N, 7.07); $\tilde{\nu}$ (KBr): 1725, 1680 cm^{-1} (CO); δ_H: 1.21 (3 H, d, *J* 3.0, 3-Me), 1.27 (3 H, t, *J* 7.3, CH_2*Me*), 1.62 (1 H, m, 3a-H), 1.84 (1 H, m, 3–H), 2.12, 2.46 (each 3 H, each s, 1- and 7–Me), 2.77 (1 H, d *J* 5.9, 2-H), 3.09 (1 H, dd, *J* 5.6, 12.2, 4-H), 3.51 (1 H, t, *J* 12.2, 4-H), 3.71 (1 H, d, *J* 4.6, 9b-H), 4.19 (2 H, q, *J* 7.3, C*H*$_2$Me), 4.32, 4.74 (each 1 H, each d, *J* 17.2, C*H*$_2$Ph), 5.74 (1 H, s, 6-H), 7.15–7.40 (5 H, Ph); δ_C ($CDCl_3$): 14.4, 20.4, 20.5, 39.5, 40.9, 49.7, 54.1, 57.0, 60.5, 60.8, 74.7, 88.8, 95.6, 125.9, 129.0 × 2, 136.2, 154.6, 161.0, 164.9, 173.6.

Thermal reaction of aldehyde **4b;** *General procedures:* a solution of aldehyde **4b** (0.30 g, 1.0 mmol) in xylene (10 ml) was heated under reflux for 24 h. Chromatographic purification on silica gel gave **9b** (0.4 g, 13%; hexane/ethyl acetate = 2/1). **8b** (0.13 g, 43%, hexane/ethyl acetate = 1/1), and **7b** (0.4 g, 14%, hexane/ethyl acetate = 1/2), respectively.

(4S*,5R*)-(±)-1-Benzyl-5-hydroxy-4,8-dimethyl-4,5-dihydropyrrolo[4,3-*b*]azepin-6(1*H*)-one (**7b**): colourless prisms from hexane-benzene; m.p. 75–76ºC (Found: 72.47; H, 6.48; N, 4.67. $C_{18}H_{19}NO_3$ requires C, 72.70; H, 6.44; N, 4.71); $\tilde{\nu}$ (KBr): 3375, (OH), 1680 cm^1 (CO); δ_H: ($CDC1_3$): 1.24 (3H, d, *J* 7.3, 4-Me), 2.08 (3 H, s, 8-*Me*), 2.77–2.81 (2 H, m, 4-H and 5-OH), 4.73 (2 H, s, C*H*$_2$Ph), 4.81 (1 H, dd, *J* 3.3, 9.6, 3-H), 5.28 (1 H, s, 5-H), 5.75 (1 H, s, 9-H), 5.91 (1 H, dd, *J* 2.3, 9.6, 2-H), 7.20-7.42 (5 H, Ph); δ_C ($CDC1_3$): 19.5, 21.8, 37.5, 55.4, 70.2, 96.9, 114.8, 126.4, 127.0, 127.8, 129.2, 130.3, 136.7, 151.0, 162.0, 162.2; *m/z* (EI): 297 (M^+).

(2*S**, 4*S**, 10*S**)-(±)-1Benzyl-7,10-dimethyl-1,2-dihydro-2,4-ethanopyrrolo[4,3-*d*][1,3]oxazin-5(4*H*,5*H*)-one (**8b**): yellow prisms from hexane-benzene; m.p. 153–157ºC (Found: 72.68; H, 6.47; N, 4.71. $C_{18}H_{19}NO_3$ requires C, 72.70; H, 6.44; N, 4.71); $\tilde{\nu}$ (KBr): 1680 cm^{-1} (CO); δ_H: ($CDC1_3$): 1.09 (3H, d, *J* 6.9, 10-Me), 1.72 (1 H, m, 10-H), 2.12 (3 H, s, 7-Me), 2.35 (1 H, dd, *J* 8.3, 13.3, 9- H), 2.65 (1 H, m, 9-H), 4.40, 4.60 (each 1 H, each d, *J*. 12.7, C*H*$_2$Ph), 4.83 (1 H, s, 4-H), 5.16 (1 H, d, *J* 5.9, 2- H), 5.66 (1 H, s, 8-H), 7.23-7.40 (5 H, Ph); δ_C ($CDC1_3$): 20.4, 21.3, 44.3, 44.4, 51.5, 79.8, 89.7, 94.9, 96.4, 126.4, 127.8, 129.0, 136.3, 150.7, 161.2, 161.8; *m/z* (EI): 297 (M^+).

1-Benzyl-4,8-dimethylpyrrolo[4,3-*b*]azepin-6(1*H*)-one (**9b**): brown needles from EtOH; m.p. 134-135ºC (Found: C, 77.51; H, 6.20; N, 4.89. $C_{18}H_{17}NO_2$ requires C, 77.39; H, 6.13; N, 5.01); ν_{max} (KBr): 1690 cm^{-1} (CO); δ_H: ($CDC1_3$): 1.76 (3H, br, s, 4-Me), 2.13 (3 H, s, 8–Me), 4.31 (2 H, s, C*H*$_2$Ph), 5.02 (1 H, d, *J* 7.6, 3-H), 5.08 (1 H, d, *J* 7.6, 2- H), 5.60 (1 H, br, s, 9-H), 6.18 (1 H, s, 5-H), 7.32 (5 H, Ph); δ_C ($CDC1_3$): 20.0, 23.5, 54.5, 99.2, 108.5, 121.4, 125.6, 127.4, 127.6, 127.8, 128.8, 135.8, 136.9, 139.4, 161.7, 163.4; *m/z* (EI): 279 (M^+).

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