π-Facial Selectivity of the 1,3-Dipolar Cycloaddition of the Parent Azomethine Ylide to Homochiral Dipolarophiles

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The 1,3-dipolar cycloaddition of the azomethine ylide (2) with homochiral cyclic dipolarophiles proceeds with high facial selectivity, whereas for homochiral acyclic dipolarophiles, the π-facial selectivity and mode of cycloaddition is dependent on the structure of the dipolarophile.
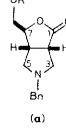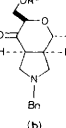
The 1,3-dipolar cycloaddition of azomethine ylides to olefinic dipolarophiles has been extensively studied [1] and has found wide applications in alkaloid syntheses.[2] Although, in contrast, the asymmetric 1,3-dipolar cycloaddition of azomethine ylides to dipolarophiles has been little studied, one recent study has reported [3] moderate diastereoselectivities for the 1,3-dipolar cycloaddition of homochiral azomet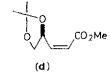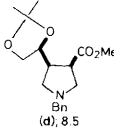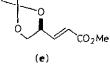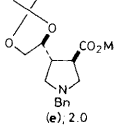hine ylides to achiral olefinic dipolarophiles. In connection with our studies on the synthesis of pyrrolidine-containing alkaloids, we decided to investigate whether or not higher diastereoselectivities would be achieved by the 1,3-dipolar cycloaddition of achiral azomethine ylides to homochiral olefinic dipolarophiles. We now report our results.

Reaction of the readily accessible [4] homochiral dipolarophiles (3a—e) with (2), which is generated from (1),[5] furnished the pyrrolidine derivatives (4a—e)† shown in Table 1. The

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† All new compounds showed satisfactory spectroscopic data. Selected data are as follows. (4a) $v_{max.}$(neat) 1 771 (CO) cm⁻¹; δ_H(400 MHz, CDCl₃) 0.95 (s, 9 H, SiMe₃), 2.33 (dd, 1 H, J 9.0, 7.0 Hz, 5-H), 2.41 (dd, 1 H, J 9.0, 7.5 Hz, 3-H), 2.70 (dd, 1 H, J 9.0, 1.5 Hz, 5¹-H), 2.87 (qqq, 1 H, J 9.0, 7.0, 4.0, 1.5 Hz, 6-H), 3.08 (dddd, 1 H, J 9.0, 7.5, 1.5, 1.5 Hz, 2-H), 3.16 (dd, 1 H, J 9.0, 1.5 Hz, 3′-H), 3.44 (d, 1 H, J 13.0 Hz, PhCH$_A$), 3.56 (dd, 1 H, J 11.0, 3.0 Hz, 8-H), 3.60 (d, 1 H, J 13.0 Hz, PhCH$_B$), 3.75 (dd, 1 H, J 11.0, 3.5 Hz, 8′-H), 4.21 (q, 1 H, J 4.0 Hz, 7-H), 7.15—7.40 (m, 11 H, PhH), and 7.55—7.60 (m, 4 H, PhH); δ_C(100 MHz, CDCl₃) 19.13, 26.70, 40.34, 45.20, 57.43, 58.75, 60.06, 65.22, 85.70, 127.09, 127.80, 128.30, 128.44, 129.88, 132.38, 132.90, 135.47, 135.62, 138.30, and 179.39; M^+, m/z 485.2371 (C₃₀H₃₅NO₃Si requires 485.2386).

(5) $v_{max.}$(neat) 1 720 (CO), 1 601, and 1 584 cm⁻¹ (C=C); δ_H(200 MHz, CDCl₃) 2.43—2.56 (m, 1 H), 2.75—3.11 (m, 5 H), 3.64 (d, 1 H, J 12.5 Hz, PhCH$_A$), 3.76 (d, 1 H, J 12.5 Hz, PhCH$_B$), 4.35—4.59 (m, 3 H), 4.65 (dd, 1 H, J 12.0, 4.0 Hz, CH₂O), 5.78—5.92 (m, 1 H, CHO), 7.20—7.62 (m, 14 H, PhH), and 7.88—8.12 (m, 6 H, PhH); δ_C(50.3 MHz, CDCl₃) 39.19, 41.20, 54.61, 57.35, 60.19, 64.35, 65.43, 71.00, 128.31, 128.40, 128.63, 129.57, 129.66, 129.92, 132.89, 133.03, 133.14, 165.53, and 166.26; M^+, m/z 563.2307 (C₃₅H₃₃NO₆ requires 563.2307).

Table 1. 1,3-Dipolar cycloaddition products ($R^1 = \text{OSiPh}_2\text{Bu}^t$ and $R^2 = \text{OSiMe}_2\text{Bu}^t$)

$$\text{Me}_3\text{SiCH}_2\underset{\overset{|}{\text{Bn}}}{\text{N}}\text{CH}_2\text{OMe} \xrightarrow[\text{CH}_2\text{Cl}_2]{\text{CF}_3\text{CO}_2\text{H}} \text{H}_2\text{C}=\overset{+}{\underset{\overset{|}{\text{Bn}}}{\text{N}}}-\overset{-}{\text{CH}}_2 \xrightarrow{(3a-e)} (4a-e)$$
$$(1) \qquad\qquad\qquad\qquad (2)$$

Compound (3)	Time (h)	Product (4)	Isolated yield (%)
(a)	2	(a)	94
(b)	2.5	(b)	77
(c)	24	No reaction	—
(d)	3	(d), 8.5 (d′), 1.5	83
(e)	5	(e), 2.0 (e′), 1.0	58

reaction of (3a,b) with (2) proceeded with very high facial selectivity and in good yield to give (4a,b), respectively. In the case of (3a), cycloaddition occurred from the side opposite to the bulky silyloxymethyl substituent and for (3b), cycloaddition proceeded from the side opposite to the anomeric ethoxy group. Disappointingly (3c) was unreactive and this closely paralleled its reported[6] inertness in the Diels–Alder reaction.

The reaction of (2) and the acyclic α,β-unsaturated esters (3d,e) was more interesting. For the cis-ester (3d), the reaction proceeded with good π-facial selectivity to give two readily separable products, (4d) and (4d'), in a combined yield of 83% and in a diastereoisomeric ratio of 8.5:1.5. Additional corroboration for the structure (4d') comes from comparing the R_f values [0.58, 7:1 (v/v) dichloromethane–acetone], as well as ^{1}H and [13]C n.m.r. spectra of the corresponding tribenzoate and the tribenzoate (5) prepared from (4a) (Scheme 1). On the other

(5)
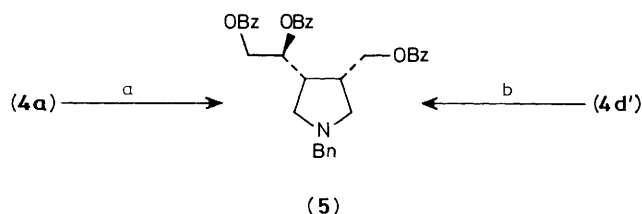
Scheme 1. *Reagents and conditions.* i, Bu$_4$NF, THF; LiAlH$_4$, THF, 65 °C; PhCOCl (3.5 equiv.), pyridine, 28 °C; ii, LiAlH$_4$, THF, 65 °C; MeOH, H$^+$; PhCOCl (3.5 equiv.) pyridine, 28 °C.

hand, the reaction of (2) and the trans-ester (3e) exhibits disappointingly lower facial selectivity; two very closely moving difficulty separable products (4e) and (4e') are formed in a combined yield of 58% and in a diastereoisomeric ratio of 2:1.

The formation of (4d) and (4d') deserves some comments. Consideration of the reactive conformers of the dipolarophile (3d) (Scheme 2) indicates that the cis-ester (3d) is forced to react
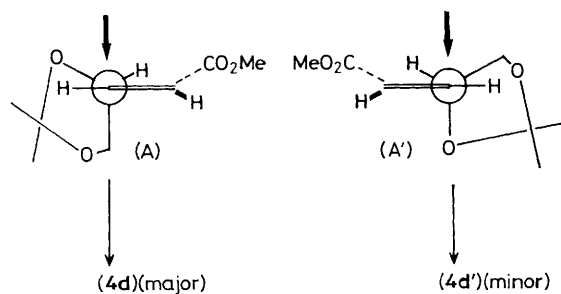
Scheme 2. Reactive conformers of compound (3d).

via the 'outside' alkoxy conformer A to give (4d) as the major product. The conformer with the more preferred 'inside' alkoxy conformation[7] is unstable due to severe non-bonded interactions between the cis methoxycarbonyl group and the dioxolane ring. The minor product (4d'), on the other hand, is formed via the conformer A' in which the allylic C–O bond is perpendicular to the plane of the π-bond. That the reaction proceeded via A' is surprising because, according to recent theoretical and experimental studies,[7] conformers such as A' are the least likely to participate in 1,3-dipolar cycloaddition reactions since this would result in unfavourable π–σ^*_{C-O} interaction in the electron-deficient transition states.

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