Pyrrolidines by 1,3-Dipolar Cycloaddition of Conjugated Azomethine Ylides

Iain Coldham,[a]* Alan J. Collis,[b] Roger J. Mould,[a] Denise E. Robinson[a]

[a] Department of Chemistry, University of Exeter, Stocker Road, Exeter EX4 4QD, England
Fax +44(1392)263434

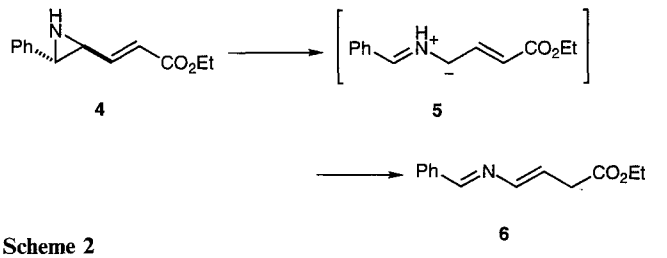
[b] Department of Discovery Chemistry, Pfizer Central Research, Sandwich, Kent CT13 9NJ, England

Received 27 February 1995

Completely *endo* selective 1,3-dipolar cycloadditions are observed between the azomethine ylide **5** and a variety of dipolarophiles. The azomethine ylide **5** can be generated by thermal ring opening of aziridine **4**. Formation of the aziridine and cycloaddition can occur smoothly in a one-pot procedure.

1,3-Dipolar cycloadditions of azomethine ylides are a well established and useful method for the synthesis of pyrrolidines.[1] One method for forming the azomethine ylide involves the thermal ring opening of an aziridine. The vast majority of cases studied use *N*-alkyl- or *N*-arylaziridines, although there are a few reports of the use of *N*-unsubstituted aziridines[2] which give the *N*-unsubstituted pyrrolidine (or pyrrole) product. Many *N*-unsubstituted pyrrolidines have important biological activity (e.g. as antivirals, anthelmintics or α-glucosidase inhibitors) and their synthesis has attracted much attention.[3] In order to stabilise the azomethine ylide, the aziridine is normally substituted in the 2-position with an anion-stabilising group such as a ketone, ester or nitrile group. While working on a variety of synthetic routes to vinylaziridines (*en route* to piperidines[4]), we discovered that a vinylogous ester group could act as the stabilising group for the azomethine ylide to give novel *N*-unsubstituted pyrrolidines after cycloaddition.

The aziridine **4** was formed from the mixtures of azido alcohols **2** and **3** using triphenylphosphine.[5] At room temperature in acetonitrile the aziridine **4** was isolated in 63% yield (Scheme 1). However, under the more normal conditions for the conversion of β-azido alcohols into aziridines by heating under reflux, the aziridine **4** was contaminated with a new product, which was characterised as the imine **6**. Thermal ring opening of the aziridine **4** to give the azomethine ylide **5** and proton-transfer would generate the imine **6** (Scheme 2). The rearrangement could be observed by ^{1}H NMR in CD_3CN and shows a gradual loss of the starting material which follows first-order kinetics with a rate constant at 70 °C of $1.4 \times 10^{-4} \pm 0.1 \times 10^{-4}\ s^{-1}$ ($t_{1/2}$ = 77 min at 70 °C). The proton transfer from the ylide **5** to give the imine **6** is presumed to be much faster than the ring opening of the aziridine **4**. On prolonged heating, the imine **6** decomposes to benzaldehyde, amongst other compounds, although the imine could be isolated in 35% yield.



Scheme 2

We were interested to discover whether the azomethine ylide **5** would undergo cycloaddition chemistry with dipolarophiles. The ylide could be represented as shown in Figure 1, in which the negative charge is delocalised over the extended conjugated system. A recent paper by Pearson[6] showed that pyrrolidines could be formed by cycloaddition of 2-azapentadienyl anions with electron-rich alkenes. The ylide **5** would be expected to react with electron-poor alkenes. There is a single report of a cycloaddition of an alkenyl-substituted azomethine ylide,[7] and heating the aziridine **4** with a range of dipolarophiles gave the expected cycloaddition products as shown in Table 1.

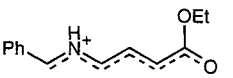
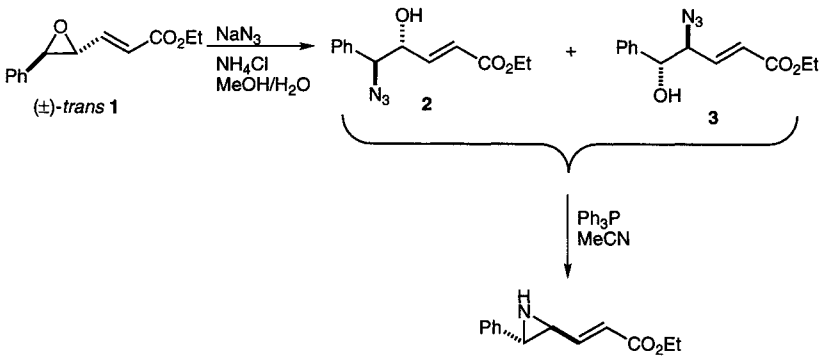


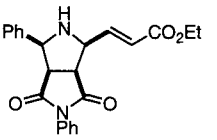
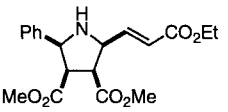
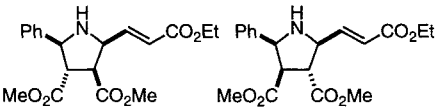
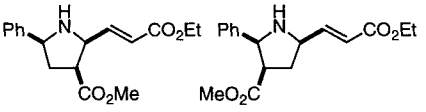
Figure 1

The optimum conditions for the cycloaddition were found to involve heating the aziridine **4** in acetonitrile with two equivalents of the dipolarophile. For example, entry 1, the cycloadduct **8** was formed in 87% yield with no trace of the *exo* product. Reducing the amount of the dipolarophile or changing the solvent lowered the yield



Scheme 1

Table 1. Cycloaddition of Azomethine ylide **5**

Entry	Dipolarophile	Reagent (equiv), solvent, time (h)	Product(s)	Yield (%)	Ratio
1	*N*-Phenylmaleimide (**7**)	**7** (2.0), MeCN, 18	 (**8**)	87	100 : 0
2	**7**	**7** (1.3), MeCN, 18	**8**	76	100 : 0
3	**7**	**7** (1.1), MeCN, 8	**8**	54	100 : 0
4	**7**	**7** (1.1), PhH, 1.5	**8**	39	100 : 0
5	**7**	**7** (1.1), PhMe, 2	**8**	47	100 : 0
6	**7**	**7** (1.1), *p*-xylene, 1.5	**8**	40	100 : 0
7	dimethyl maleate (**9**)	**9** (2.0), MeCN, 4	 **10**	63	100 : 0
8	dimethyl fumarate (**11**)	**11** (1.3), MeCN, 2.5	 **12a** **12b**	83	67 : 33
9	methyl acrylate (**13**)	**13** (2.0), MeCN, 3	 **14a** **14b**	44[a]	63 : 37

[a] The imine **6** was isolated in 16% yield.

of the cycloadduct (entries 2–6). The *endo* product was also observed with dimethyl maleate **9** (entry 7). With dimethyl fumarate **(11)** as the dipolarophile, a mixture of the two stereoisomers **12a** and **12b** was isolated. The ratio of products was determined from the ^{1}H NMR of the inseparable mixture of **12**, and the structure determination was carried out using decoupling and NOE experiments. With the unsymmetrical dipolarophile methyl acrylate **(13)**, a mixture of the regioisomers **14a** and **14b** was isolated, both of which correspond to the *endo* product.

In all cases the aziridine **4** opens in a conrotatory manner to give the W-dipole from the *trans* aziridine. On cycloaddition this generates the *cis*-2,5-disubstituted pyrrolidine. The *endo* cycloaddition products were observed in all examples and no traces of any *exo* isomers could be detected. In addition, there appears to be a slight preference (approximately 2:1) in favour of the *endo* regioisomer with the ester group from the dipolarophile vicinal to the vinyl group.

On establishing that acetonitrile was the preferred solvent for the cycloaddition, and recognising that the synthesis of the aziridine **4** involved treating the azido alcohols **2** and **3** with Ph_3P in acetonitrile, it was envisaged that both aziridine formation and cycloaddition could be accomplished in a one-pot operation. An improvement in the overall yield for the two steps and an increase in simplicity was achieved by treating the mixture of azido alcohols **2** and **3** with one equivalent of Ph_3P in MeCN at room temperature (bubbles of N_2 gas can be observed), followed by, after 3 h, addition of two equivalents of the dipolarophile **7** and heating under reflux for 18 h. Re-

Table 2. ^1H and ^{13}C NMR Data for Products **8**, **10**, **12**, **14**[a]

Product	^1H NMR ($CDCl_3$) δ, J (Hz)	^{13}C NMR ($CDCl_3$) δ
8	7.50–7.28 (8H, m, Ph), 7.30 (1H, dd, J = 16, 6, NCCH=C), 7.20–7.14 (2H, m, Ph), 6.17 (1H, dd, J = 16, 1, C=CHCO), 4.68–4.60 (1H, m, PhCH), 4.22 (2H, q, J = 7, OCH_2), 4.19–4.13 (1H, m, NCHC=), 3.58–3.49 (2H, m, OCCHCHCO), 1.31 (3H, t, J = 7, CH_3)	174.2, 173.7, 165.8, 144.3, 137.4, 129.0, 128.4, 128.3, 127.2, 126.2, 122.8, 64.5, 60.8, 60.5, 49.6, 49.2, 14.2
10	7.38–7.20 (5H, m, Ph), 7.16 (1H, dd, J = 16, 7, NCCH=), 6.06 (1H, dd, J = 16, 1, C=CHCO), 4.52 (1H, d, J = 6, PhCH), 4.24–4.20 (1H, m, NCHC=), 4.19 (2H, q, J = 7, OCH_2), 3.66 (3H, s, OMe), 3.62–3.52 (2H, m, OCCHCHCO), 3.26 (3H, s, OMe), 2.28 (1H, br s, NH), 1.29 (3H, t, J = 7, CH_2CH_3)	171.4, 170.7, 166.1, 145.1, 137.7, 128.3, 127.7, 126.9, 123.5, 65.3, 60.6, 52.6, 51.9, 51.3, 14.2
12	7.52–7.20 (10H, m, Ph), 7.15 (1H, dd, J = 16, 6, $NCCH^b$=), 6.93 (1H, dd, J = 16, 6, $NCCH^a$=), 6.16 (1H, dd, J = 16, 1, $=CH^bCO$), 6.09 (1H, dd, J = 16, 1, $=CH^aCO$), 4.65 (1H, d, J = 9, $PhCH^b$), 4.34 (1H, d, J = 9, $PhCH^a$), 4.25–4.19 (1H, m, NCH^aC=), 4.22 (2H, q, J = 7, OCH_2^b), 4.18 (2H, q, J = 7, OCH_2^a), 4.06–3.98 (1H, m, NCH^bC=), 3.72 (3H, s, OMe^b), 3.68–3.62 (1H, m, $PhCCH^b$), 3.66 (3H, s, OMe^a), 3.64–3.57 (1H, m, $=CCCH^a$), 3.62 (3H, s, OMe^a), 3.44 (1H, dd, J = 9, 6, $PhCCH^a$), 3.36 (1H, dd, J = 9, 6, $=CCCH^b$), 3.14 (3H, s, OMe^b), 2.10 (2H, br s, NH), 1.29 (3H, t, J = 7, $CH_2CH_3^b$), 1.26 (3H, t, J = 7, $CH_2CH_3^a$)	173.1, 172.6, 172.2, 171.9, 166.2, 165.9, 146.6, 144.3, 140.4, 138.8, 128.6, 128.1, 128.0, 127.8, 127.3, 127.1, 122.9, 122.6, 66.5, 64.6, 62.2, 61.3, 60.5, 60.4, 54.5, 53.4, 52.4, 52.3, 52.1, 52.0, 51.4, 14.2, 14.2
14	7.50–7.18 (10H, m, Ph), 7.12 (1H, dd, J = 16, 6, $NCCH^b$=), 6.96 (1H, dd, J = 16, 6, $NCCH^a$=), 6.11 (1H, dd, J = 16, 1, $=CH^bCO$), 6.10 (1H, dd, J = 16, 1, $=CH^aCO$), 4.58 (1H, d, J = 9, $PhCH^b$), 4.24–4.20 (1H, m, $PhCH^a$), 4.22 (2H, q, J = 7, OCH_2^b), 4.19 (2H, q, J = 7, OCH_2^a), 4.17–4.10 (1H, ddd, J = 8, 6, 1, NCH^aC=), 3.96–3.87 (1H, m, NCH^bC=), 3.65 (3H, s, OMe^a), 3.40–3.27 (2H, m, CH_2CO_2Me), 3.16 (3H, s, OMe^b), 2.40 (1H, ddd, J = 13, 8, 7, $PhCCH^a$ *trans* to Ph), 2.30–2.12 (3H, m, $PhCCH^a$ *cis* to Ph and $PhCCH_2^b$), 2.02 (2H, br s, NH), 1.32 (3H, t, J = 7, $OCH_2CH_3^b$), 1.28 (3H, t, J = 7, $OCH_2CH_3^a$)	173.4, 173.1, 166.4, 166.1, 148.7, 145.6, 142.2, 139.9, 128.5, 127.9, 127.5, 127.1, 126.9, 122.5, 121.4, 64.9, 62.7, 61.6, 60.4, 60.3, 59.0, 51.7, 51.2, 49.8, 48.6, 37.4, 34.7, 14.3, 14.2

[a] All products gave satisfactory high resolution mass spectra.

moval of the solvent and purification by column chromatography gave the *endo* adduct **8** in 76% yield for the two-step procedure.

Reagents were obtained from commercial suppliers and were used without further purification. All reactions were conducted under an atmosphere of argon. MeCN was distilled over calcium hydride and stored over 4 Å molecular sieves. Flash chromatography was performed using silica gel (230–400 mesh). Mps were determined on an Electrothermal melting point apparatus and are uncorrected. Mass spectra and high resolution mass spectra were obtained using a Kratos Profile instrument. IR spectra were recorded on a Perkin-Elmer 881 spectrophotometer. ^1H NMR were obtained on a Bruker AM300 (300 MHz) instrument and ^{13}C NMR on a Bruker AM300 (75.5 MHz) instrument. J values are given in Hz.

Ethyl (*E*)-3-[(2*S*,3*S*)- and (2*R*,3*R*)-3-Phenylaziridin-2-yl]prop-2-enoate (4) and Ethyl (*E*,*E*)-6-Phenyl-5-azahexa-3,5-dienoate (6):
PPh_3 (934 mg, 3.58 mmol) was added to a mixture of the azido alcohols **2** and **3**[4] (890 mg, 3.41 mmol) in MeCN (25 mL) under argon at r.t. After 3 h the solvent was evaporated under reduced pressure and the residue was purified by column chromatography on silica gel; petroleum ether (bp 40–60 °C)–EtOAc, 4:1), to give the aziridine **4** (467 mg, 63%) as an oil, R_f 0.20 (hexane–EtOAc, 4:1).

IR ($CHCl_3$): ν = 3310 (NH), 1710 (C=O), 1650 (C=C), 1605 and 1495 cm^{-1} (Ph).

^1H NMR ($CDCl_3$): δ = 7.42–7.17 (5H, m, Ph), 6.71–6.52 (1H, m, CH=CCO), 6.08 (1H, d, J = 15.5, CHCO), 4.23 (2H, q, J = 7, OCH_2), 3.08 (1H, br s, PhCH), 2.60 (1H, br s, PhCCH), 1.35 (1H, br s, NH), 1.29 (3H, t, J = 7, CH_3).

^{13}C NMR ($CDCl_3$): δ = 165.9, 147.4, 138.4, 128.6, 127.6, 125.7, 122.3, 60.5, 42.6, 41.9, 14.2.

HRMS: Found M^+, 217.1106. $C_{13}H_{15}NO_2$ requires M, 217.1103.

MS: m/z = 217 (24%, M), 172 (13%, M – OEt), 144 (100%, M – CO_2Et).

Heating the reaction under reflux for 90 min (instead of stirring at room temperature) gave the aziridine **8** (36%) as an oil, data as above, and the imine **6** (35%) as an oil, R_f 0.57 (hexane–EtOAc, 3:1).

IR ($CHCl_3$): ν = 1730 (C=O), 1645 (C=C), 1605 (C=N), 1600, 1575 and 1490 cm^{-1} (Ph).

^1H NMR ($CDCl_3$): δ = 8.21 (1H, s, PhCH), 7.84–7.78 (2H, m, Ph), 7.47–7.37 (3H, m, Ph), 6.88 (1H, dt, J = 7, 1.5, NCH=C), 5.65 (1H, q, J = 7, NC=CH), 4.18 (2H, q, J = 7, OCH_2), 3.70 (2H, dd, J = 7, 1.5, CH_2CO), 1.28 (3H, t, J = 7, CH_3).

^{13}C NMR ($CDCl_3$): δ = 171., 160.8, 142.6, 136.3, 131.1, 128.7, 128.6, 121.6, 60.5, 32.4, 14.2.

HRMS: Found M^+, 217.1094. $C_{13}H_{15}NO_2$ requires M, 217.1103.

MS: m/z = 217 (30%, M), 144 (100%, M – CO_2Et), 104 (59%, PhCHN).

Ethyl (*E*)-3-[(1*R*,2*R*,4*S*,5*S*)- and (1*S*,2*S*,4*R*,5*R*)-6,8-Dioxo-2,7-diphenyl-3,7-diazabicyclo[3.3.0]octan-4-yl)]prop-2-enoate (8); Typical Procedure:
The aziridine **4** (50.5 mg, 0.233 mmol) and *N*-phenylmaleimide (82.5 mg, 0.476 mmol) in dry MeCN (3 mL) were heated under reflux under argon for 18 h. The solvent was removed under reduced pressure and the residue was purified by column chromatography on silica gel; petroleum ether (bp 40–60 °C)–EtOAc–CH_2Cl_2, 1:1:1 to give the cycloadduct **8** (79 mg, 87%) which was recrystallized from hexane–CH_2Cl_2 to give needles, mp 158–160 °C.

We thank the SERC for an Earmarked Studentship (to R.J.M.) and Pfizer Central Research for a CASE Award (to R.J.M.). We also thank Exeter University Research Fund for a summer research assistant (to D.E.R.) and Dr. Vladimir Sik for NMR experiments.

(1) Lown, J.W. In *1,3-Dipolar Cycloaddition Chemistry*; Padwa, A., Ed.; Wiley: New York, 1984.
Vedejs, E. In *Advances in Cycloaddition*, Ed.; Curran, D.P.; JAI: Greenwich, Connecticut, 1988.
Padwa, A. In *Comprehensive Organic Synthesis*; Trost, B.M.; Fleming, I., Eds.; Pergamon: 1991, Vol. 4, Chap. 4.9, p 1069.
Wade, P.A. In *Comprehensive Organic Synthesis*; Trost, B.M.; Fleming, I., Eds.; Pergamon: 1991, Vol. 4, Chap. 4.10, p 1111.

(2) Padwa, A.; Hamilton, L. *Tetrahedron Lett.* **1965**,4363.
Gelas-Mialhe, Y.; Touraud, E.; Vessiere, R. *Can. J. Chem.* **1982**, *60*, 2830.
See also: Grigg, R.; Montgomery, J.; Somasunderam, A. *Tetrahedron* **1992**, *48*, 10431.
(3) For some recent references, see:
Hirai, Y.; Terada, T.; Amemiya, Y.; Momose, T. *Tetrahedron Lett.* **1992**, *33*, 7893.
Myerscough, P.M.; Fairbanks, A.J.; Jones, A.H.; Bruce, I.; Choi, S.S.; Fleet, G.W.J.; Al-Daher, S.S.; Cenci di Bello, I.; Winchester, B. *Tetrahedron* **1992**, *48*, 10177.
Horikawa, M.; Hashimoto, K.; Shirahama, H. *Tetrahedron Lett.* **1993**, *34*, 331.
Wang, Y.-F.; Takaoka, Y.; Wong, C.-H. *Angew. Chem., Int. Ed. Engl.* **1994**, 1242.
Baldwin, J.E.; Rudolph, M. *Tetrahedron Lett.* **1994**, *35*, 6163.
Panday, S.K.; Griffart-Brunet, D.; Langlois, N. *Tetrahedron Lett.* **1994**, *35*, 6673.
Oppolzer, W.; Bochet, C.G.; Merifield, E. *Tetrahedron Lett.* **1994**, *35*, 7015.
Moody, C.M.; Young, D.W. *Tetrahedron Lett.* **1994**, *35*, 7277.
(4) Coldham, I.; Collis, A.J.; Mould, R.J.; Rathmell, R.E. *Tetrahedron Lett.* **1995**, *36*, 3557.
(5) The azido alcohols **2** and **3** were prepared from the epoxide **1** in a similar way to that reported by: Wipf, P.; Fritch, P.C. *J. Org. Chem.* **1994**, *59*, 4875.
See also: Satake, A.; Shimizu, I.; Yamamoto, A. *Synlett* **1995**, 64.
(6) Pearson, W.H.; Jacobs, V.A. *Tetrahedron Lett.* **1994**, *35*, 7001.
(7) Bourhis, M.; Vercauteren, J. *Tetrahedron Lett.* **1994**, *35*, 1981.