



0957-4166(95)00198-0

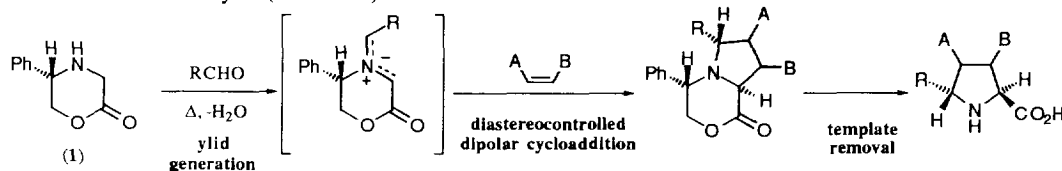
## Synthesis of Carboxylated Pyrrolidine Derivatives *via* 1,3-Dipolar Cycloadditions of Homochiral Double-Stabilised *E*-Azomethine Ylids.

L. M. Harwood\* and I. A. Lilley

Dyson Perrins Laboratory, University of Oxford, South Parks Road, Oxford OX1 3QY, U.K.

**Abstract:** The preparation and subsequent diastereoselective 1,3-dipolar cycloaddition of *E*-carboethoxy-substituted azomethine ylids derived by condensing 5-(*S*)-phenylmorpholinone (**1**) with ethyl glyoxalate is described. Removal of the chiral template furnishes enantiomerically pure pyrrolidine-2,5-dicarboxylate derivatives.

In a series of papers we have reported that 5-phenylmorpholin-2-one reacts with aldehydes under both thermal<sup>1</sup> and catalysed conditions,<sup>2</sup> generating azomethine ylid species capable of undergoing highly diastereoselective cycloadditions. Subsequent removal of the chiral template permits the generation of proline derivatives in high enantiomeric purity. Intramolecular reactions in which the dipolarophile is tethered to the aldehyde used to generate the ylid proceed with high control of the reacting ylid geometry;<sup>3</sup> whilst intermolecular reactions of alkene dipolarophiles with aldehydes other than formaldehyde show moderate selectivity for reaction *via* the *E*-azomethine ylid (**Scheme 1**).<sup>1c</sup>

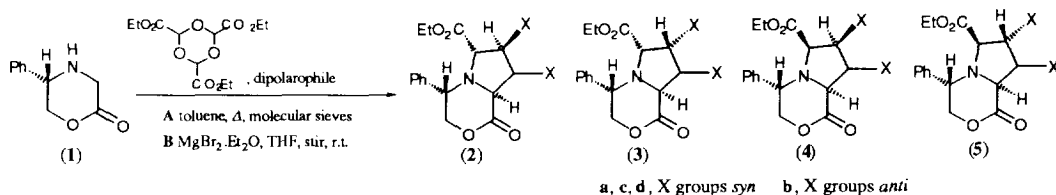


Scheme 1

We now wish to report the results of our investigations into the diastereoselectivity of the cycloaddition reaction of the azomethine ylid derived from the condensation of 5-(*S*)-phenylmorpholin-2-one with ethyl glyoxalate in which an additional electron withdrawing group stabilises the dipole as well as introducing possibilities for geometric isomerism.

5-(*S*)-Phenylmorpholin-2-one (**1**), ethyl glyoxalate trimer and a representative range of alkene dipolarophiles were heated to reflux in toluene, with azeotropic removal of water.<sup>1</sup> Removal of solvent and column chromatography allowed the cycloadducts to be isolated and analysis of the 2-dimensional and n.o.e difference spectra permitted unambiguous configurational assignment in each instance (**Scheme 2, conditions A**).<sup>4</sup> Having demonstrated that ethyl glyoxalate would react with (**1**) to form a substituted ylid capable of

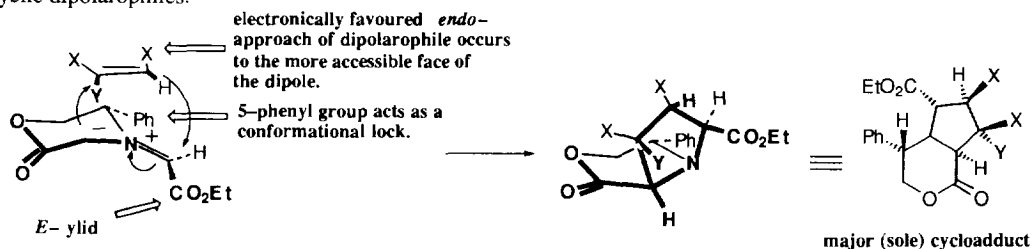
undergoing diastereoselective intermolecular trapping under thermal conditions with various dipolarophiles, the same conversions were studied under Lewis acid catalysis.<sup>2</sup> Accordingly the same reactions were repeated at room temperature in THF with  $\text{MgBr}_2 \cdot \text{Et}_2\text{O}$  and molecular sieves. Standard work-up and purification furnished the same cycloadducts as in the thermal conditions (**Scheme 2, conditions B**).



dipolarophile	isolated yield (%)							
	(2)		(3)		(4)		(5)	
	A	B	A	B	A	B	A	B
 a	37	44	0	0	0	0	0	0
 b	44	65	0	0	0	0	0	0
 Z = NPh c	28	32	1	17	9	0	0	0
 Z = NMe d	25	23	6	33	0	0	0	0

**Scheme 2**

In keeping with our previous observations and rationale, the major (or sole) products (**2a–d**) were shown to result from exclusive trapping of the *E*-ylid occurring with *endo*-approach of the dipolarophile to the least-hindered face of the templated ylid locked in a conformation in which the phenyl group is equatorial (**Figure**). Catalysis results in a uniform increase in material yield of adducts derived solely from the *E*-ylid but reduced diastereocontrol leading to the formation of greater quantities of *exo*-adducts (**3c, d**) in the case of the cyclic dipolarophiles.

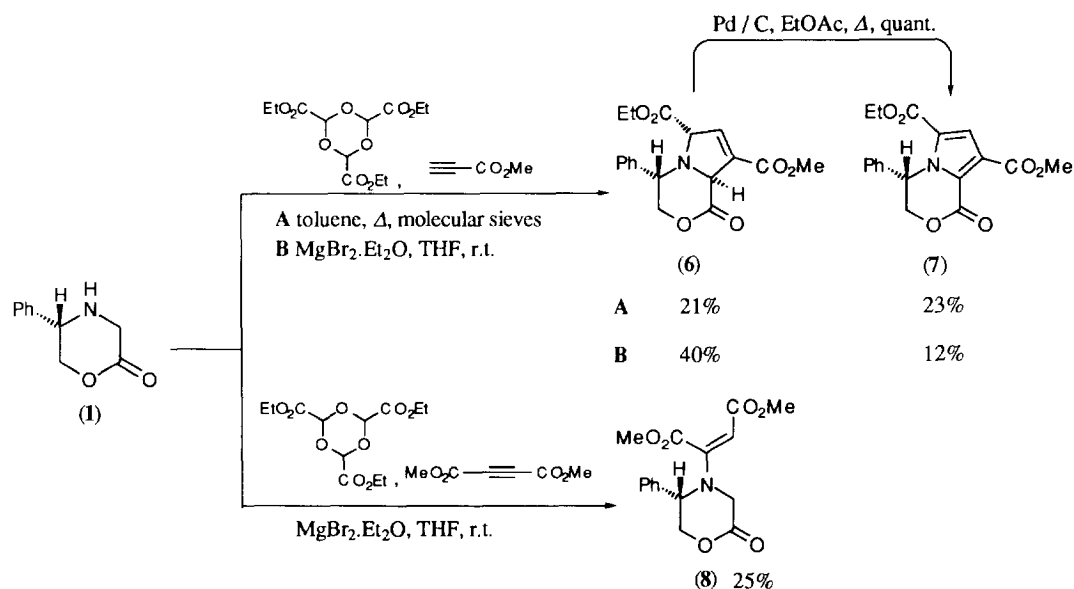


**Figure**

Although the diastereocontrol is better than previously found for intermolecular trapping of substituted ylids, the combined yields of cycloadducts are generally lower than those observed in the corresponding reactions of the formaldehyde derived ylid.<sup>1c</sup> Both observations presumably reflect the lower reactivity of the ylid due to the additional electron withdrawing effect of the carboethoxy substituent. Notably, dimethyl fumarate and dimethyl maleate furnish a single cycloadduct (**2a, 2b** respectively) under thermal and catalysed conditions.

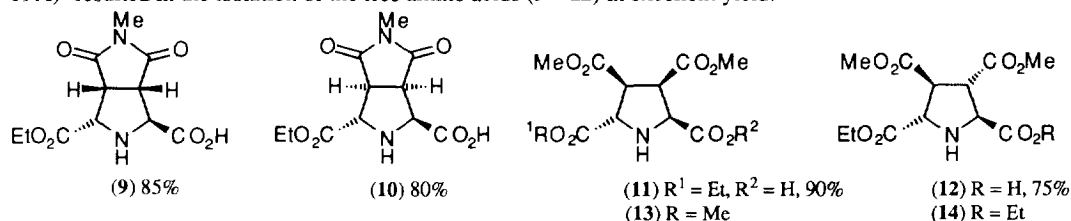
Cycloadducts with alkyne dipolarophiles are free from stereochemical complications arising from *exo*- or *endo*- attack. Accordingly dimethyl acetylenedicarboxylate and methyl propiolate were heated with 5-(*S*)-phenylmorpholin-2-one (**1**) and ethyl glyoxylate trimer in refluxing toluene with azeotropic removal of water. Although dimethyl acetylenedicarboxylate was found to be unreactive under these conditions, methyl propiolate was found to give two products corresponding to the desired cycloadduct (**6**) and the pyrrole (**7**) (Scheme 3). The stereo- and regiochemistry of (**6**) were determined by COSY and n.O.e difference experiments,<sup>4</sup> and found to be in accordance with our previous observations.<sup>1c</sup> The structure of pyrrole (**7**) was confirmed by quantitative dehydrogenation of cycloadduct (**6**) with palladium on charcoal in refluxing ethyl acetate.<sup>3b</sup>

Under the catalysed conditions, dimethyl acetylenedicarboxylate was again found not to produce the desired cycloadduct, but underwent Michael addition to furnish adduct (**8**). However, methyl propiolate did react to give the cycloadduct (**6**) in improved yield accompanied by lesser amounts of the pyrrole (**7**).



Scheme 3

Subjecting cycloadducts (**2** – **5**) to catalytic hydrogenolysis (Pearlman's catalyst,  $\text{H}_2$  5 bar, MeOH, TFA)<sup>5</sup> resulted in the isolation of the free amino acids (**9** – **12**) in excellent yield.



Treatment of (**11**) with methanolic HCl resulted in formation of the corresponding tetramethyl ester (**13**) as its hydrochloride salt; whereas reaction of (**12**) under the same conditions led to a mixture of products. However, treatment of (**12**) with excess EtI,  $\text{K}_2\text{CO}_3$  in acetone at room temperature gave the diethyl dimethyl ester (**14**) in which the symmetry resulting from the 2-fold rotational axis was clearly demonstrated by the simplicity of the  $^1\text{H}$  and  $^{13}\text{C}$  NMR spectra.<sup>4</sup>

## ACKNOWLEDGEMENTS

We thank the E.P.S.R.C. for a postgraduate studentship to I.A.L.

## REFERENCES

- 1 (a) Anslow, A.S.; Harwood, L.M.; Phillips, H.; Watkin, D.J.; *Tetrahedron Asymmetry*, 1991, **2**, 169; ; *Tetrahedron Asymmetry*, 1991, **2**, 997. Anslow, A.S.; Harwood, L.M.; Phillips, H.; Watkin, D.J.; Wong, L.F.; *Tetrahedron Asymmetry*, 1991, **2**, 1343. Harwood, L.M.; Macro, J.; Watkin, D.J.; Williams, C. E.; Wong, L.F.; *Tetrahedron Asymmetry*, 1992, **3**, 1127. For related studies in this area see: Williams, R. M.; Zhai, W.; Aldous, D. J.; Aldous, S. C. *J. Org. Chem.*, 1992, **57**, 6527. Baldwin, J. E.; MacKenzie, S. C.; Moloney, M. *SYNLETT*, 1994, 926.
- 2 Harwood, L.M.; Manage, A.C.; Robin, S.; Hopes, S.F.G.; Watkin, D.J.; Williams, C.E.; *SYNLETT* 1993, 777.
- 3 (a) Harwood, L.M.; Lilley, I.A.; *Tetrahedron Lett.*, 1993, **34**, 537; (b) Harwood L.M. Kitchen, L.C.; *Tetrahedron Lett.*, 1993, 6603.
- 4 All novel compounds isolated had spectroscopic data in accord with their assigned structures. Selected data: **2a** M.p.=179–180°C; found C, 58.24, H, 6.13, N, 3.56 C<sub>20</sub>H<sub>23</sub>NO<sub>8</sub> requires C, 58.01, H, 5.89, N, 3.56;  $\nu_{\max}$  (KBr) 1758, 1740, 1732, 1719 cm<sup>-1</sup>;  $\delta_{\text{H}}$  (500MHz, CDCl<sub>3</sub>) 7.29–7.39 (m, 5H, Ph), 4.68 (d, *J* 6.2, 1 H, 6 $\alpha$ -H), 4.40 (dd, *J* 10.7, *J'* 2.4, 1 H, 2 $\beta$ -H), 4.35 (t, *J* 10.7, 1 H, 3 $\alpha$ -H), 4.25 (dd, *J* 10.7, *J'* 2.4, 1 H, 3 $\beta$ -H), 4.02 (d, *J* 10.2, 1 H, 9 $\beta$ -H), 3.83 (t, *J* 6.7, 1 H, 7 $\alpha$ -H), 3.73–3.79 (m, 1 H), 3.75 (s, 3 H), 3.67 (s, 3 H), 3.57 (dd, *J* 10.2, *J'* 7.1, 1 H, 8 $\alpha$ -H), 3.35–3.42 (m, 1 H), 0.88 (t, *J* 7.1, 3 H); ; n.O.e expt 4.70 6 $\alpha$ -H–7 $\alpha$ -H (13.2%), –8 $\alpha$ -H (5.6%), 4.00 9 $\beta$ -H–2 $\beta$ -H (8.3%), –8 $\alpha$ -H (1%);  $m/z$  (CI, NH<sub>3</sub>) 406 (M+H), 332, 104;  $[\alpha]_{\text{D}}^{25} +68.1$  (c 0.31, CHCl<sub>3</sub>); **2b** M.p.=99–100°C; found C, 58.18, H, 5.69, N, 3.27 C<sub>20</sub>H<sub>23</sub>NO<sub>8</sub> requires C, 58.01, H, 5.89, N, 3.56;  $\nu_{\max}$  (KBr) 1762, 1740, 1728 cm<sup>-1</sup>;  $\delta_{\text{H}}$  (500MHz, C<sub>6</sub>D<sub>6</sub>) 6.98–7.15 (m, 5H, Ph), 4.69 (d, *J* 5.0, 1 H, 6 $\alpha$ -H), 4.33 (dd, *J* 6.9, *J'* 5.0, 1 H, 7 $\beta$ -H), 4.03 (t, *J* 6.8, 1 H, 8 $\alpha$ -H), 3.79 (d, *J* 6.7, 1 H, 9 $\beta$ -H), 3.72 (dd, *J* 10.9, *J'* 4.0, 1 H, 2 $\beta$ -H), 3.51–3.60 (m, 3 H), 3.36 (s, 3 H), 3.32–3.38 (m, 1 H), 3.26 (s, 3 H), 0.63 (t, *J* 7.1, 3 H); n.O.e. 4.70 6 $\alpha$ -H→7 $\alpha$ -H (3.3%), →8 $\alpha$ -H (1.2%), 4.35 7 $\beta$ -H→8 $\alpha$ -H (2.5%), →6 $\alpha$ -H (2.3%), →9 $\beta$ -H (1.5%), 3.80 9 $\beta$ -H→2 $\beta$ -H (5.4%);  $m/z$  (CI, NH<sub>3</sub>) 406 (M+H), 104 ;  $[\alpha]_{\text{D}}^{25} -27.9$  (c 0.61, CHCl<sub>3</sub>); **6** M.p.=120–123°C; found C, 62.84, H, 5.32, N, 3.80 C<sub>18</sub>H<sub>19</sub>NO<sub>6</sub> requires C, 62.60, H, 5.55, N, 4.06;  $\nu_{\max}$  (KBr) 1757, 1751, 1724, 1646 cm<sup>-1</sup>;  $\delta_{\text{H}}$  (500MHz, CDCl<sub>3</sub>) 7.29–7.49 (m, 5H, Ph), 6.72 (t, *J* 1.7, 1 H, 8-H), 5.30 (dd, *J* 5.9, *J'* 1.6, 1 H, 6 $\alpha$ -H), 4.42 (dd, *J* 5.9, *J'* 1.9, 1 H, 9 $\beta$ -H), 4.25–4.37 (m, 2 H), 4.05 (dd, *J* 10.8, *J'* 3.9, 1 H, 2 $\beta$ -H), 3.85 (s, 3 H), 3.78–3.85 (m, 1 H), 3.64–3.70 (m, 1 H), 0.90 (t, *J* 7.1, 3 H); n.O.e. 6.70 8-H→9 $\beta$ -H (7%), 4.40 9 $\beta$ -H→2 $\beta$ -H (10%), →8-H (7.7%);  $m/z$  (CI, NH<sub>3</sub>) 346 (M+H), 344, 272, 104;  $[\alpha]_{\text{D}}^{25} -136$  (c 0.29, CHCl<sub>3</sub>); **13** M.p.>310°C;  $\nu_{\max}$  (KBr) 3436, 1748, 1635 cm<sup>-1</sup>;  $\delta_{\text{H}}$  (500MHz, D<sub>2</sub>O) 4.99 (s, 1 H), 4.97 (d, *J* 4.7, 1 H), 4.17 (t, *J* 7.0, 1 H), 4.09 (dd, *J* 9.9, *J'* 7.6, 1 H), 3.80 (s, 3 H), 3.79 (s, 3 H), 3.75 (s, 3 H), 3.69 (s, 3 H);  $\delta_{\text{C}}$  (500MHz, D<sub>2</sub>O) 171.0, 169.8, 167.9, 166.9, 62.2, 60.0, 54.78, 54.0, 54.2, 48.9, 48.6;  $m/z$  (CI, NH<sub>3</sub>) 304 (MH<sup>+</sup>), 244, 80;  $[\alpha]_{\text{D}}^{25.5} +4.1$  (c 0.27, MeOH); **14**  $\nu_{\max}$  (thin film) 3341, 1739 cm<sup>-1</sup>;  $\delta_{\text{H}}$  (500MHz, CDCl<sub>3</sub>) 4.19–4.27 (m, 6 H), 3.76 (s, 6 H), 3.66 (dd, *J* 4.3, *J'* 1.8, 2 H), 2.90 (bs, 1 H), 1.29 (t, *J* 7.1, 3 H);  $\delta_{\text{C}}$  (500MHz, CDCl<sub>3</sub>) 171.9, 171.7, 62.9, 61.7, 52.7, 50.9, 14.1;  $m/z$  (CI, NH<sub>3</sub>) 332 (M+H), 226;  $[\alpha]_{\text{D}}^{25.5} +10.8$  (c 0.74, CHCl<sub>3</sub>).
- 5 Cox, G. G.; Harwood, L. M.; *Tetrahedron Asymm.* 1994, **5**, 1669.