Pergamon

Tetrahedron Letters 39 (1998) 475–478

TETRAHEDRON LETTERS

Cycloadditions of Aromatic Imines to Enantiomerically Pure Stabilized Azomethine Ylids: Construction of *threo* (2*S*, 3*R*)-3-Aryl-2,3-diamino Acids

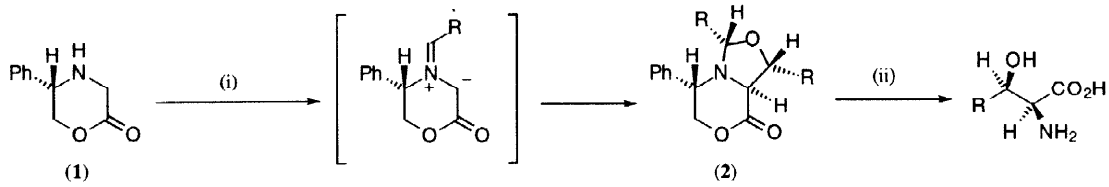
David Alker,[a] Laurence M. Harwood[b]* and C. Eleri Williams[c]

[a] Pfizer Ltd, Central Research, SANDWICH CT13 9NJ, U. K.
[b]Department of Chemistry, University of Reading, Whiteknights, READING RG6 6AD, U.K.
[c]Dyson Perrins Laboratory, University of Oxford, South Parks Road, Oxford OX1 3QY, U.K.

Received 24 September 1997; revised 5 November 1997; accepted 7 November 1997

Abstract: Chiral stabilized azomethine ylids derived from reaction of (5*S*)–phenylmorpholin-2-one (**1**) with aromatic imines undergo efficient and highly diastereocontrolled cycloaddition with a second molecule of imine to furnish products which may be converted into enantiomerically pure *threo* (2*S*, 3*R*)–3–aryl–2,3–diamino acids.

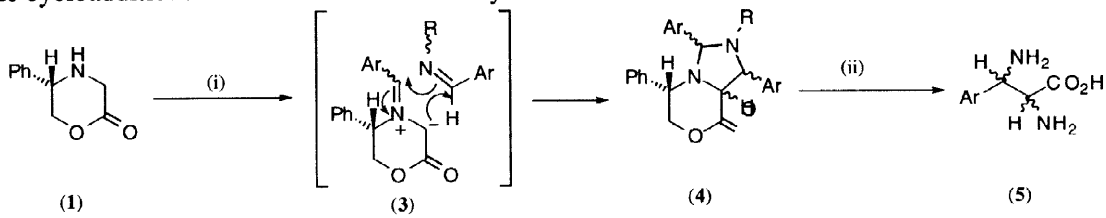
We have demonstrated (5*S*)–phenylmorpholin-2-one (**1**) to be a versatile precursor template for the generation of chiral azomethine ylids. Subsequent trapping of the reactive intermediate is possible with a range of electron deficient alkene or alkyne dipolarophiles[1] whilst, in the absence such a dipolarophile, a second molecule of aldehyde will participate in diastereocontrolled 1,3–dipolar cycloaddition with the *E*-ylid to form cycloadducts (**2**) (**Scheme 1**) in good to excellent yields. These cycloadducts may be subsequently converted into enantiomerically pure *threo* (2*S*, 3*R*)–2–amino–3–hydroxy acids.[2]



Reagents and conditions: (i) RCHO (3 equiv.), solvent, Δ. (ii) H_2–$Pd(OH)_2$, TFA, aq MeOH (R = aryl)

Scheme 1

Imines have been to reported act in an analogous manner to aldehydes and undergo cycloadditions with various 1,3–dipoles.[3] We decided to explore the possibility that use of an excess of aromatic imine would result in initial condensation with morpholin-2-one (**1**) to generate an azomethine ylid (**3**) followed by cycloaddition of the ylid with a second molecule of imine (**Scheme 2**) to ascertain if the diastereocontrol observed in the case of aldehyde cycloadditions would also hold for this system.



Reagents and conditions: (i) ArCH=NR' (excess), solvent, Δ ; (ii) hydrogenolysis

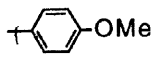
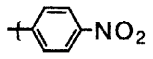
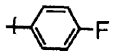
Scheme 2

0040-4039/98/$19.00
PII: S0040-4039(97)10580-9

Subsequent degradation of the cycloadduct would furnish 2,3–diamino acids useful as dipeptide replacements[4] and components of peptidic inhibitors of aminopeptidases.[5] This is a largely overlooked class of non–proteinogenic amino acids and far less effort has been directed towards developing stereocontrolled methodology for constructing 2,3–diamino acids compared to other amino acid systems.[6] The potential for diastereocontrol in our enantiomerically pure system therefore prompted us to investigate this process further.

Initial attempts to effect this reaction were carried out with *S*–(**1**) and *N*-methylbenzaldimine, but no cycloaddition was observed under conditions previously successful with aldehydes. However, due to the earlier reports that imines will act as dipolarophiles,[2] we reasoned that failure of the process lay in the lack of generation of the azomethine ylid due to insufficient electrophilicity of the imine. In an attempt to render the imine more electrophilic, one equivalent of pyridinium *p*-toluenesulfonate was added to the mixture, resulting in disappearance of starting material (toluene, reflux, 3h) and the formation of a single product, as indicated by t.l.c. and spectroscopic analysis of the crude mixture. Spectroscopic analysis of the purified material, obtained in 56% yield after chromatography on silica, eluting with hexane–ethyl acetate (4 : 1), indicated it to have the gross structure of the desired cycloadduct (**4**) and the relative stereochemistry was demonstrated by n.O.e. difference spectroscopy to be as depicted in **Scheme 3**.[7]

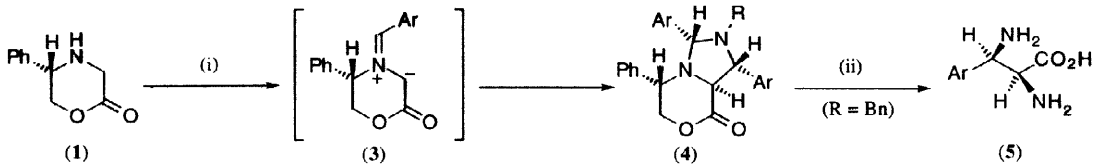
Following this observation it was decided to investigate the generality of this methodology using *N*–benzyl imines, as hydrogenolysis of the ensuing cycloadducts would afford free 2,3–diamino acids directly. Hence, a series of aromatic *N*–benzyl imines was subjected to the same reaction conditions and, in each case, resulted in a single diastereoisomeric cycloadduct as judged by detailed analysis of the crude reaction mixture. Purification by column chromatography as before permitted isolation of the pure cycloadducts (**4a–e**) as yellow foams in good to excellent yield (**Table**).

	Ar	R	Cycloadduct (**4**)		Amino acid (**5**)	
			Purified yield (%)	$[\alpha]_D$ ($CHCl_3$)	Purified yield (%)	$[\alpha]_D$ (H_2O)
a		Me	56	–103.6		
b		Bn	43	–31.5	83 [ref 6a]	– 0.9
c		Bn	65	–59.8	81 [ref 6b]	–14.6
d		Bn	57	–43.5	66*	–5.2
e		Bn	70	–49.0	64	–7.8

*Concomitant reduction of the nitro– group during hydrogenolysis furnished 3–(4–aminophenyl)–2,3–diaminopropanoic acid (**5d**)

Table

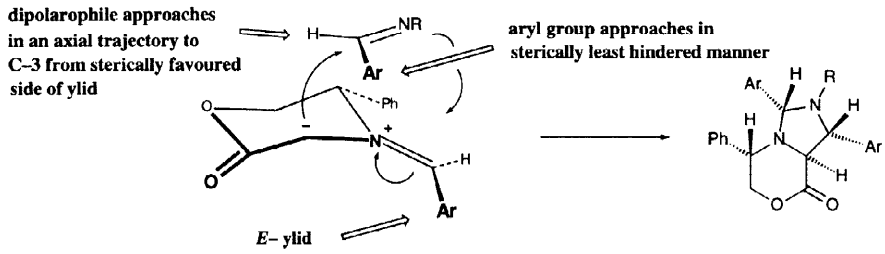
The relative stereochemistry of each adduct was confirmed by n.O.e. difference studies (mutual enhancements amongst H2, H7 and H9 proving particularly diagnostic) and reflected the stereochemistry observed for (**4a**).[7] Hydrogenolysis of these adducts under acidic conditions released the corresponding *threo* (2*S*,3*R*)–3–aryl–2,3–diamino acids (**5b–e**) in excellent yields, purification being achieved by basic ion-exchange chromatography on Dowex® 1X8-200 (Dowex-1-chloride) (**Scheme 3, Table**).[8]



Reagents and conditions: (i) ArCH=NR (3 equiv), pyridinium *p*–toluenesulfonate (1 equiv.), toluene, Δ; (ii) $Pd(OH)_2$, H_2 (5 bar), TFA, MeOH–H_2O (10:1)

Scheme 3

The stereochemical course of the cycloaddition thus follows an analogous pathway to that observed in the aldehyde cycloaddition reactions,[2] and can be rationalized by the same model of sterically directed approach of the dipolarophilic component in an axial manner to C–3 of the *E*–configurated ylid (**Figure**).



Figure

In conclusion, we have demonstrated that aromatic imines will undergo Brønsted acid induced condensation with (*S*)–(**1**) to furnish chiral azomethine ylids which undergo diastereocontrolled 1,3–dipolar cycloaddition with excess imine to furnish cycloadducts (**4a–e**). Subsequent hydrogenolysis of *N*–benzyl adducts (**4b–e**) leads to isolation of enantiomerically pure *threo* (2*S*,3*R*)–3–aryl–2,3–diamino acids (**5**).

Acknowledgement: We thank Pfizer Central Research, EPSRC and the DTI for financial support of this work under the auspices of the Asymmetric LINK Scheme (to C.E.W.).

References

1. Alker, D.; Harwood, L. M.; Williams, C. E. *Tetrahedron*, **1997**, *53*, 12671 and references cited therein.
2. Harwood, L. M.; Macro, J.; Watkin, D.; Williams, C. E.; Wong, L. F. *Tetrahedron :Asymm.*, **1992**, 1127.
3. For example see: Ito, K.; Saito, K.; Takahashi, K. *Heterocycles*, **1993**, *36*, 21; Marrs, C. M. ; Trost, B. M. *J. Am. Chem. Soc.*, **1993**, *115*, 6636; Chastanet, J.; Roussi, G. *J. Org. Chem*, **1988**, *53*, 3808.
4. Mohan, R.; Chou, Y. L.; Bihovsky, R.; Lumma, W. C. *J. Med. Chem.*, **1991**, *34*, 2402.
5. Herranz, R.; Vinuesa, S.; Castro–Pichel, J. Perez, C., Garcia–Lopez, M. T. *J. Chem. Soc., Perkin Trans 1*, **1992**, 1825.
6. For example see: (a) Ali, R. M.; Khan, N. H. *Synth. Commun.*, **1978**, *8*, 497 (b) Rakshinda, M. A.; Khan, N.H. *Synth Commun.*, **1979**, *9*, 351; 360 (c) Arnold, L. D.; Kalantar, T. H.; Vederas, J. C. *J. Am. Chem. Soc.*, **1985**, *107*, 7105 (d) Dunn, P. J.; Häner, R., Rapoport, H. *J. Org. Chem.*, **1990**, *55*, 5017 (e) Pfammatter, E.; Seebach, D. *Ann. Chem.*, **1991**, 1323 (f) Es–Sayed, M.; Gratowski, C.; Krass, N.; Meyers, A.; de Meijere, A. *Synlett*, **1992**, 963 (g) Bellus, D.: Ernst, B.; Gonda, J.; Helland, A–C. *Synthesis*, **1993**, 1323 (h) Burke, A. J.; Davies, S. G.; Hedgecock, C. J. *Synlett*, **1996**, 621.
7. (**4a**) m.p. 118-120 °C; Found C, 78.22, H, 6.53, N, 7.25 %, $C_{25}H_{24}N_2O_2$ requires C, 78.09, H, 6.30, N, 7.29 %; ν_{max} (KBr disc) 1748 cm^{-1}; δ_H (500 MHz, C_6D_6) 7.99 (d, *J* 7.1 Hz, 2H), 7.41 (t, *J* 7.7 Hz, 2H), 7.28 (t, *J* 7.4 Hz, 1H), 6.98-6.94 (m, 4H), 6.90- 6.87 (m, 4H), 6.80-6.78 (m, 2H), 4.36 (d, *J* 6.8 Hz, 1H), 3.92 (d, *J* 6.8 Hz, 1H), 3.68 (m, 1H), 3.67 (s, 1H). 3.64 (dd, *J* 11.7 Hz, *J'* 10.0 Hz), 3.54 (dd,

J 10.0 Hz, *J'* 4.3 Hz, 1H), 1.91 (s, 3H); n.O.e. **H2** → H9 (12.7%), **H7** → H9 (4.3%); δ_C (50.3 MHz, $CDCl_3$) 172.0, 141.0, 139.1, 137.4, 129.4, 128.8, 128.6, 128.4, 128.1, 127.8, 91.8, 70.9, 70.8, 65.7, 61.7, 36.3; $^m/_z$ (CI, NH_3) 385 (MH^+) 266; $[\alpha]_D$ –103.6 (c 1.0, $CHCl_3$). (**4b**) m.p. 45-48 °C; ν_{max} (KBr disc) 1752 cm^{-1}; δ_H (500 MHz, C_6D_6) 7.85 (d, *J* 7.0 Hz, 2H), 7.30-7.27 (m, 4H), 7.00-6.87 (m, 9H), 6.82-6.79 (m, 3H), 6.69-6.67 (m, 2H), 4.73 (d, *J* 6.1 Hz, 1H), 4.05 (s, 1H), 3.82 (d, *J* 6.1 Hz, 1H), 3.62 (d, *J* 14.1 Hz, 1H), 3.53 (dd, *J* 11.8, *J'* 4.8 Hz, 1H), 3.49 (dd, *J* 11.8, *J'* 9.8 Hz, 1H), 3.45 (d, *J* 14.1 Hz, 1H), 3.31 (dd, *J* 9.9, *J'* 4.9 Hz, 1H); n.O.e. **H7** → H9 (5.3 %), → H2 (4.4 %), **H9** → H2 (12.7 %); δ_C (50.3 MHz, $CDCl_3$) 171.6, 141.1, 139.2, 137.3, 135.0, 130.4, 129.7, 129.0, 128.7, 128.5, 128.4, 128.0, 127.9, 127.8, 127.5, 127.4, 127.3, 87.0, 71.0, 66.0, 65.7, 61.4, 51.2; $^m/_z$ (DCI, NH_3) 461 (MH^+), 266; $C_{31}H_{29}N_2O_2$ requires 461.2229, found 461.2221; $[\alpha]_D^{20}$ -31.5 (c 1.0, $CHCl_3$). (**4c**) m.p. 48-51 °C; Found C, 78.22, H, 6.53, N, 7.25 %, $C_{33}H_{32}N_2O_4$ requires C, 78.09, H, 6.30, N, 7.29 %; δ_H (500 MHz, $CDCl_3$) 7.80 (d, *J* 8.6 Hz, 2H), 7.19 (d, *J* 8.6 Hz, 2H), 7.05-7.02 (m, 4H), 6.99-6.95 (m, 1H), 6.94 (d, *J* 8.6 Hz, 2H), 6.86-6.81 (m, 3H), 6.74-6.72 (m, 2H), 6.55 (d, *J* 8.6 Hz, 2H), 4.70 (d, *J* 6.2 Hz, 1H), 4.05 (s, 1H), 3.88 (d, 6.2 Hz, 1H), 3.70 (d, *J* 14.1 Hz, 1H), 3.54 (d, *J* 13.8 Hz, 1H), 3.38 (s, 3H), 3.33 (dd, *J* 8.9, *J'* 5.6 Hz, 1H), 3.24 (s, 3H); n.O.e. **H9** → H2 (10.4%), → H7 (4.8%); $^m/_z$ (DCI, NH_3) 520 (MH^+) 296, 226; $[\alpha]_D^{22}$ -59.8 (c 0.5, $CHCl_3$). (**4d**) m.p. 68-70 °C; ν_{max} (KBr disc) 1 751 cm^{-1}; δ_H (500 MHz, $CDCl_3$) 7.99 (d, *J* 8.7 Hz, 2H), 7.65 (d, *J* 8.6 Hz, 2H), 7.47 (d, *J* 8.7 Hz, 2H), 6.89 (d, *J* 8.6 Hz, 2H), 6.87-6.82 (m, 3H), 6.71-6.64 (m, 5H), 6.46 (m, 2H), 4.42 (d, *J* 6.6 Hz, 1H), 3.80 (s, 1H), 3.56 (d, *J* 6.6 Hz, 1H), 3.51 (dd, *J* 11.9, *J'* 10.5 Hz, 1H) 3.46 (dd, *J* 12.0, *J'* 4.3 Hz, 1H), 3.26 (d, *J* 13.8 Hz, 1H), 3.15 (d, *J* 13.8 Hz, 1H); n.O.e. **H7** → H2 (5.3%), → H9 (4.4%), **H9** → H2 (13.8%); $^m/_z$ (DCI, NH_3) 551 (MH^+), 281, 211, 31; $C_{31}H_{27}N_4O_6$ requires 551 1931, found 551.1972; $[\alpha]_D^{24}$ -43.5 (c 0.85, $CHCl_3$). (**4e**) m.p. 53-55 °C; Found C, 75.07, H, 5.37, N, 5.41 %, $C_{31}H_{26}N_2O_2F_2$ requires C, 74.83, H, 5.47, N, 5.63 %; ν_{max} (KBr disc) 1 751 cm^{-1}; δ_H (500 MHz, $CDCl_3$) 7.60 (dd, *J* 8.6, *J* 5.5 Hz, 2H), 7.01-6.92 (m, 7H), 6.84-6.77 (m, 5H), 6.60-6.55 (m, 4H), 4.56 (d, *J* 6.3 Hz, 1H), 3.87 (s, 1H), 3.66 (d, *J* 6.3 Hz, 1H) 3.51-3.48 (m, 2H), 3.47 (d, 13.7 Hz, 1H), 3.32 (d, *J* 14.0 Hz, 1H), 3.20 (dd, *J* 8.1, *J* 6.7 Hz, 1H); n.O.e. **H2** → H9 (11.0%), **H7** → H9 (4.6%); δ_C (125.7 Hz, $CHCl_3$) 171.6, 130.1, 136.6, 135.3, 134.9, 131.3, 130.3, 130.1, 128.2, 128.1, 127.9, 127.7, 127.4, 115.8, 115.3, 114.9, 114.5, 86.7, 71.1, 65.8, 65.4, 61.7, 51.5; $^m/_z$ (CI, NH_3) 497 (MH^+),$[\alpha]_D^{20}$ -49.0 (c 1.0, $CHCl_3$).

8. (**5b**) δ_H (500 MHz, D_2O) 7.48-7.25 (m, 5H), 4.64 (d, *J* 5.2 Hz, 1H), 4.64 (d, *J* 5.2 Hz, 1H); δ_C (125.7 MHz, D_2O) 169.3, 151.7, 129.8, 128.8, 126.9, 53.0, 52.4; $^m/_z$ (CI, NH_3) 181 (MH^+), $C_9H_{13}N_2O_2$ requires 181.0977, found 181.0979; $[\alpha]_D^{24}$ –0.9 (c 1.0, H_2O). (**5c**) m.p. 185-186°C (dec.); δ_H (500 MHz, D_2O) 7.37 (d, *J* 8.8Hz, 2H), 7.05, (d, *J* 8.7 Hz, 2H), 4.66 (d, *J* 5.1 Hz, 1H), 4.15 (d, *J* 5.1 Hz, 1H), 3.82 (s, 3H); δ_C (125.7 MHz, D_2O) 170.1, 159.4, 128.5, 122.1, 114.2, 54.5, 53.5, 52.3; $^m/_z$ (Electrospray) 211 (MH^+), 150, $C_{10}H_{15}N_2O_3$ requires 211.1083, found 211.1071; $[\alpha]_D^{25}$ –14.6 (c 1.0, H_2O). (**5d**) Pale yellow powder; ν_{max} (KBr disc) 3431, 1679 1631 cm^{-1}; δ_H (500 MHz, D_2O) 7.25 (d, *J* 8.5 Hz, 2H), 6.88 (d, *J* 8.5 Hz, 2H), 4.66 (d, *J* 4.8 Hz, 1H), 4.23 (d, *J* 4.9 Hz, 1H); $^m/_z$ (CI, NH_3) $C_9H_{14}N_3O_2$ requires 196.1086, found 196.1089; $[\alpha]_D^{24}$ –5.2 (c 0.25, H_2O). (**5e**) m.p. 190-195 °C (dec.); δ_H (500 MHz, D_2O) 7.47-7.42 (m, 2H), 7.23 (t, *J* 8.8Hz, 2H), 4.77 (d, *J* 4.9 Hz, 1H), 4.23 (d, *J* 4.9 Hz, 1H); δ_C (125.7 MHz, D_2O) 171.1, 131.1, 130.6, 128.3, 117.1, 54.7, 53.4; $^m/_z$ (DCI, NH_3) 199 (MH^+), 124, $C_9H_{12}N_2O_2F$ requires 199.0883, found 199.0892; $[\alpha]_D^{25}$ –7.8 (c 0.5, H_2O).