COMMUNICATION

Diastereocontrolled Strecker reaction using (*S*)-5-phenylmorpholin-2-one

Laurence M. Harwood,*[a] Michael G. B. Drew,[a] David J. Hughes[b] and Richard J. Vickers[a]

[a] *Department of Chemistry, University of Reading, Whiteknights, Reading, UK RG6 6AD. E-mail: l.m.harwood@reading.ac.uk; Fax: 44 (0)1189 316782; Tel: 44 (0)1189 318449*

[b] *Syngenta, Jealott's Hill International Research Centre, Bracknell, Berkshire, UK RG42 6EY. E-mail: dave.hughes@syngenta.com; Fax: 44 (0)1344 41373 9; Tel: 44 (0)1344 414962*

Received (in Cambridge, UK) 9th May 2001, Accepted 1st June 2001
First published as an Advance Article on the web 27th June 2001

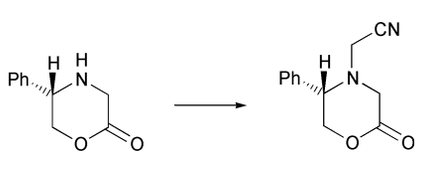
Iminium ions derived from (*S*)-5-phenylmorpholin-2-one 1 undergo diastereoselective Strecker reactions using copper(I) cyanide and anhydrous hydrochloric acid; the major adducts may be degraded to D-α-amino acids.

Introduction

(*S*)-5-Phenylmorpholin-2-one **1**† has proven to be a highly versatile template for the induction of stereocontrol during diastereoselective reactions of azomethine ylides in the synthesis of proline derivatives,[1] β-hydroxy-α-amino acids,[2] and α,β-diamino acids.[3] In addition, we have revealed that the 3,4-didehydro derivatives undergo diastereocontrolled alkylation.[4] Furthermore, iminium species generated *in situ* from **1** undergo diastereoselective Mannich reactions with 2-furylboronic acid and subsequent chemical manipulation of the adducts has yielded a range of enantiopure α-amino acids.[5a,b]

Results and discussion

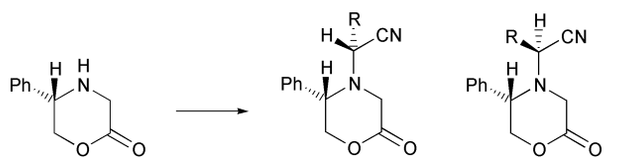
In efforts to extend the diastereoselective Mannich protocol, our attention turned to alternative nucleophiles that would demonstrate increased atom efficiency over the furan nucleus as a carboxy equivalent and, to this end, attention focused on attempts to develop a diastereocontrolled Strecker reaction.[6] Reagents previously used as cyanide sources, such as TMS-CN,[6a,e] KCN,[6b] and $EtAl_2CN$,[6c] did not promote the desired reaction, but it was found that copper(I) cyanide in the presence of aqueous hydrochloric acid and paraformaldehyde furnished the desired parent adduct **2** in 78% yield (Scheme 1).



Scheme 1 *Reagents and conditions*: CuCN, HCl, $(CH_2O)_n$, THF, rt.

Disappointingly, when aldehydes other than paraformaldehyde were subjected to these conditions, only low yields of the desired adducts were observed. However, exposure of **1** to a range of aldehydes in the presence of CuCN and anhydrous sodium sulfate in THF containing anhydrous HCl, led to the isolation of diastereoisomeric Strecker adducts **3** and **4** in good combined yield, reaction being complete within a few minutes at room temperature (Scheme 2).

Unfortunately, diastereocontrol over the reaction was poor with the ratio of diastereoisomers **3** : **4** being approximately 2.5 : 1. However, by conducting the reaction in THF at reflux for 2 hours it was found that the diastereomeric ratio improved to around 12 : 1 in favour of isomer **3** (Table 1); the isomers being readily separated by column chromatography. ‡§



Scheme 2 *Reagents and conditions*: CuCN, HCl (anhyd.), Na_2SO_4 (anhyd.), RCHO, THF.

Table 1 Isolated yields of Strecker adducts

R	**3**	**4**	Diastereoisomeric ratio **3** : **4**
*i*Pr	79	6	13.2 : 1 [a]
*n*Bu	77	5	15.4 : 1 [a]
*i*Bu	76	6	12.5 : 1 [a]
$PhCH_2CH_2$	76	6	12.7 : 1 [a]
Ph	64	5	12.8 : 1 [a]
4-$(NO_2)C_6H_4$	58	5	11.6 : 1 [a]
Cyclopropyl	38	17	2.2 : 1 [b]
Me	42	19	2.2 : 1 [b]

[a] Reaction carried out in refluxing THF. [b] Reaction carried out at room temperature.

The reaction protocol successfully accommodated both aryl and alkyl aldehydes, although attempts with ketones met with failure, and electron-rich aryl aldehydes, such as anisaldehyde, gave low yields of adducts. In the cases of cyclopropylcarbaldehyde and acetaldehyde, the necessity of conducting the reaction at room temperature led to the lower diastereoisomeric ratios, although yields of adducts were acceptable.

Structure determination *via* X-ray crystallographic analysis of adduct **3a** confirmed the relative configurations of the major isomers as having the (*R*)-configuration at the newly formed exocyclic stereocentre (Fig. 1).¶

It appears that the major diastereoisomers **3** are favoured both thermodynamically and kinetically, although our mnemonic for predicting stereocontrol holds true for each case (Fig. 2).

With a series of adducts in hand, attention focused on removal of the template and hydrolysis of the nitrile to release the desired α-amino acids. Although we have reported a template degradation protocol that could have been adapted to the present system,[5b] we desired a more expedient route. Reduction of the lactone **3a** with DIBAL-H furnished lactol **5** in quantitative yield as a 1 : 2 mixture of anomers. Dehydration to furnish enamine **6** in 54% yield was achieved with acetic anhydride in the presence of excess of $BF_3{\cdot}OEt_2$[7] (Scheme 3). Attempts at hydrolysis of the enamine **6** failed and thus a one-pot oxidative procedure was developed. A DCM solution of enamine **6** and MCPBA was stirred for 10 hours before the addition of periodic acid and water. After stirring for a further 10 hours

DOI: 10.1039/b104052a

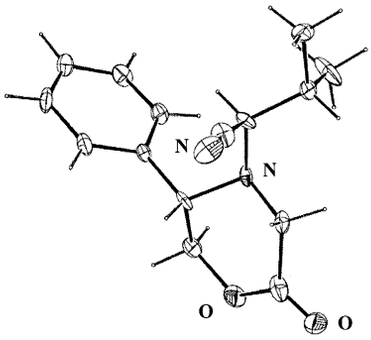


Fig. 1 X-Ray structure of major adduct **3a**.

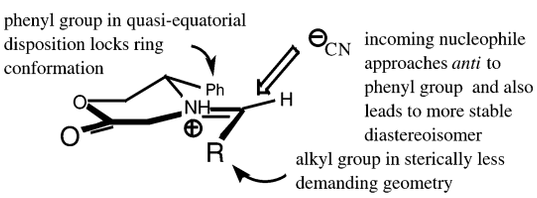
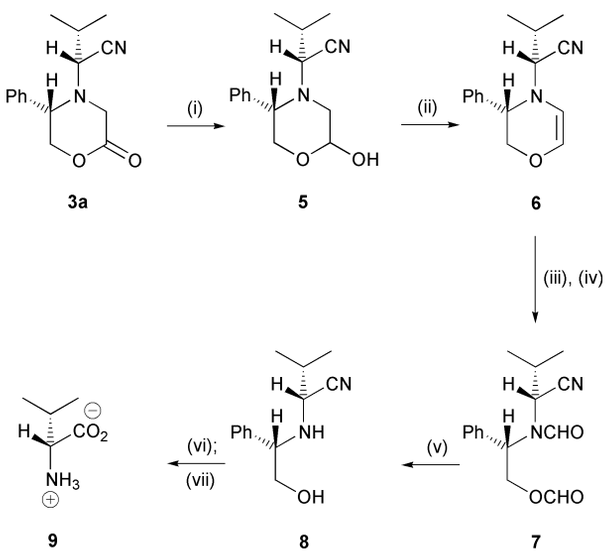


Fig. 2 Stereochemical rationale.



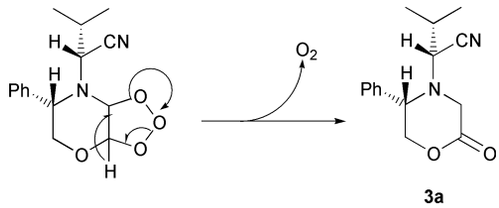
Scheme 3 *Reagents and conditions*: (i) DIBAL-H, THF, −78 °C; (ii) Ac_2O, BF_3·OEt_2, MeCN, rt; (iii) MCPBA, DCM; (iv) H_5IO_6; (v) EtOH, $TiCl_4$, rt; (vi) $Pb(OAc)_4$, MeOH–DCM, 0 °C; (vii) conc. HCl.

7 was isolated in 84% yield and this was most efficiently deformylated by stirring in ethanol in the presence of $TiCl_4$, delivering the amino alcohol **8** in 95% yield. Following a procedure developed by Chakraborty,[8] the amino alcohol **8** was oxidized with lead(IV) acetate to the imine, which, without isolation, was subjected to reflux in concentrated HCl. Following purification by ion-exchange chromatography, D-valine **9** was isolated in 74% yield (32% overall yield from **3a**). On the basis of the specific rotation {$[a]_D^{20}$ −25.9 (*c* 4.0, 6 M HCl), lit.[6b] $[a]_D^{20}$ −26.02 (*c* 4.0, 6 M HCl)} the final amino acid had been obtained without compromising the integrity of the stereocentre of **3a** during degradation.

Alternative attempts at ozonolytic cleavage of **6** furnished **7** in only 23% yield with the major product being **3a**, isolated in 48% yield. Lactone **3a** could arise *via* 1,2-shift of H-2 of the molozonide to carbon (or oxygen *via* intermediacy of the enol) with concomitant loss of molecular oxygen (Scheme 4).

Conclusions

We have demonstrated that Strecker adducts can be prepared in high yield with good diastereocontrol using (*S*)-5-phenylmorpholin-2-one **1**, aldehydes, copper(I) cyanide and anhydrous HCl. The reaction successfully accommodates both



Scheme 4

aryl and alkyl aldehydes and template degradation has been illustrated with adduct **3a** to release (*R*)-D-valine in 32% overall yield. During the course of the template degradation crude reaction mixtures can be carried through the process without detrimental effects.

Experimental

Typical experimental procedure for preparation of adducts 3 and 4

To a rapidly stirred solution of morpholinone **1** (1 mmol, 1.0 equiv.) in THF (18 mL) under a nitrogen atmosphere were added sequentially HCl (4 M in 1,4-dioxane, 275 μL, 1.1 equiv.), CuCN (2 mmol, 2.0 equiv.) and anhydrous Na_2SO_4 (890 mg). The requisite aldehyde (5 mmol, 5.0 equiv.) was then added and the mixture heated to reflux for 2 hours before Et_3N (0.89 mL) was added. The suspension was then cooled to room temperature before diethyl ether (18 mL) was added and the reaction filtered through a short silica pad. The pad was washed with ether and, following solvent removal under reduced pressure, the residual oil was purified by flash column chromatography on silica, typically eluting with 1 : 1 diethyl ether–petrol to separate the diastereoisomeric products.

Selected data

Compound 3a. Colourless solid, mp 91–93 °C; $[a]_D$ +75.0 (*c* 0.56, $CHCl_3$); ν_{max} (Nujol) 1760 cm^{-1}; δ_H (250 MHz, $CDCl_3$) 7.31–7.27 (5H, m), 4.30–4.20 (2H, m), 3.82 (1H, dd, *J* 4.1, *J′* 10.0 Hz), 3.73 (1H, d, *J* 17.5 Hz), 3.43 (1H, d, *J* 17.5 Hz), 2.95 (1H, d, *J* 11.2 Hz), 1.95–1.80 (1H, m), 0.92 (6H, d, *J* 6.6 Hz); δ_C (69.2 MHz, $CDCl_3$) 166.8, 134.5, 130.1, 130.0, 128.8, 115.9, 72.8, 61.7, 60.7, 49.2, 28.6, 20.5, 19.1; $C_{15}H_{19}N_2O_2$ (MH^+) requires 259.1447, found 259.1440.

Compound 4a. Colourless solid, mp 126–131 °C; $[a]_D$ +183.0 (*c* 0.94, $CHCl_3$); ν_{max} (Nujol) 1752 cm^{-1}; δ_H (250 MHz, $CDCl_3$) 7.27–7.31 (5H, m), 4.47 (1H, dd, *J* 4.3, *J′* 11.8 Hz), 4.30 (1H, dd, *J* 6.2, *J′* 11.8 Hz), 4.10 (1H, dd, *J* 4.3, *J′* 6.2 Hz), 3.79 (1H, d, *J* 16.1 Hz), 3.64 (1H, d, *J* 16.1 Hz), 3.10 (1H, d, *J* 10.3 Hz), 1.45–1.50 (1H, m), 0.91 (3H, d, *J* 6.6 Hz), 0.72 (3H, d, *J* 6.6 Hz); δ_C (69.2 MHz, $CDCl_3$) 168.6, 138.1, 129.4, 129.2, 128.1, 117.4, 71.4, 65.0, 59.8, 52.5, 30.2, 20.3, 20.0; $C_{15}H_{19}N_2O_2$ (MH^+) requires 259.1447, found 259.1451.

Acknowledgements

We thank Syngenta for a CASE studentship to R.J.V.

Notes and references

† The trivial morpholinone nomenclature is used in this report for the 1,4-oxazinan-2-one ring system.

‡ All novel compounds in this report gave spectroscopic and analytical data in accord with their assigned structures.

§ The product ratios were based on isolated yields and, where resolution permitted, were found to be in close agreement with analysis of signal intergrations in the ^1H NMR of the crude reaction mixtures.

¶ X-Ray crystal data: **3a**, $C_{15}H_{18}N_2O_2$, *M* = 258.31, monoclinic, space group $P2_1$, *Z* = 2, *a* = 9.599(12), *b* = 6.542(8), *c* = 12.017(14), *β* = 99.61(10)°, *U* = 744 Å^3, *ρ* = 1.153 g cm^{-3}, 1584 independent reflections were collected with MoK*α* radiation on the MARresearch Image Plate

system. Data analysis was carried out with the XDS program;[9] the structure was solved by direct methods using SHELX86[10] and refined on F^2 using SHELX[11] to R 1 0.0686, wR 2 0.1937 on 1112 observed data. Atomic co-ordinates, bond lengths and angles and thermal parameters have been deposited with the Cambridge Crystallographic Data Centre. CCDC reference number 163541. See http://www.rsc.org/suppdata/p1/b1/b104052a/ for crystallographic files in .cif or other electronic format.

1 A. S. Anslow, L. M. Harwood and I. A. Lilley, *Tetrahedron: Asymmetry*, 1995, **6**, 2465; L. M. Harwood, A. C. Manage, S. Robin, S. F. G. Hopes, D. J. Watkin and C. E. Williams, *Synlett*, 1993, 777; L. M. Harwood and I. A. Lilley, *Tetrahedron: Asymmetry*, 1995, **6**, 1557.

2 D. Alker, G. Hamblett, L. M. Harwood, S. M. Robertson, D. Watkin and C. E. Williams, *Tetrahedron*, 1998, **54**, 6089; L. M. Harwood and S. M. Robertson, *Chem. Commun.*, 1998, 2641.

3 D. Alker, L. M. Harwood and C. E. Williams, *Tetrahedron Lett.*, 1998, **39**, 475.

4 L. M. Harwood, S. N. G. Tyler, A. S. Anslow, I. D. MacGilp and M. G. B. Drew, *Tetrahedron: Asymmetry*, 1997, **8**, 4007.

5 (*a*) L. M. Harwood, G. S. Currie, M. G. B. Drew and R. W. A. Luke, *Chem. Commun.*, 1996, 1953; (*b*) G. S. Currie, M. G. B. Drew, L. M. Harwood, D. J. Hughes, R. W. A. Luke and R. J. Vickers, *J. Chem. Soc., Perkin Trans. 1*, 2000, 2982.

6 For other examples of asymmetric Strecker reactions in the synthesis of α-amino acids see: (*a*) H. Kunz and W. Sager, *Angew. Chem., Int. Ed. Engl.*, 1987, **26**, 557; H. Kunz, H. W. Sager, W. Pfrengle and D. Schanzenbach, *Tetrahedron Lett.*, 1988, **29**, 4397; (*b*) T. Inaba, I. Kozono, M. Fujita and K. Ogura, *Bull. Chem. Soc. Jpn.*, 1992, **65**, 2359; (*c*) F. A. Davies and D. L. Fanelli, *J. Org. Chem.*, 1998, **63**, 1981; (*d*) K. Saito and S. Harada, *Tetrahedron Lett.*, 1989, **30**, 4535; (*e*) T. K. Chakraborty, K. Hussain and G. V. Reddy, *Tetrahedron*, 1995, **33**, 9179; (*f*) M. S. Iyer, K. M. Gigstad, N. D. Namdev and M. Lipton, *J. Am. Chem. Soc.*, 1996, **118**, 4910; (*g*) C. A. Krueger, K. W. Kuntz, C. D. Dzeiebra, W. G. Wirschum, J. D. Gleason, M. L. Snapper and A. H. Hoveyda, *J. Am. Chem. Soc.*, 1999, **121**, 4284.

7 R. M. Williams and Y. Aoyagi, *Tetrahedron*, 1998, **54**, 10419.

8 T. K. Chakraborty, G. V. Reddy and K. Azharttursein, *Tetrahedron Lett.*, 1991, **32**, 7579.

9 W. Kabsch, *J. Appl. Crystallogr.*, 1988, **21**, 916.

10 G. M. Sheldrick, *Acta Crystallogr., Sect. A: Fundam. Crystallogr.*, 1990, **46**, 467.

11 G. M. Sheldrick, 1993, Program for crystal structure refinement, University of Göttingen.