Pergamon

Tetrahedron Letters 39 (1998) 6029–6032

TETRAHEDRON LETTERS

Stereoselectivity in amidyl radical cyclisations. Acyl mode cyclisations.

Andrew J. Clark*, and Joanne L. Peacock

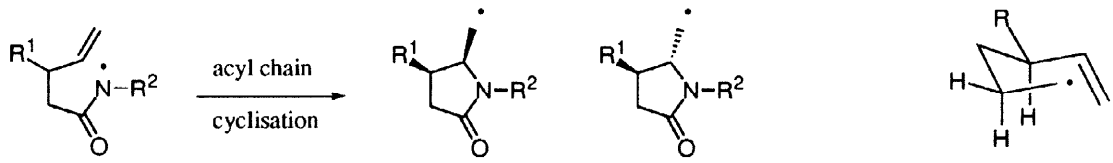
Department of Chemistry, University of Warwick, Coventry, CV4 7AL, UK.

Received 20 May 1998; accepted 8 June 1998

Abstract: Amidyl radicals generated from tributylstannane mediated homolysis of *O*-benzoyl hydroxamic acid derivatives undergo 5-exo cyclisation to give mixtures of *cis* and *trans* pyrrolidinones. While the steric nature of the nitrogen substituents investigated had little effect on the diastereoselectivity of the process they did effect the relative rate of the cyclisation reactions. The major products could be predicted by application of the "Beckwith rule".

Keywords: stereochemistry; hydroxamic acid derivatives; radical reactions; pyrrolidinones.

In recent years intramolecular radical additions to alkenes have been developed, and these represent a powerful tool for the construction of cyclic arrays.[1-4] While the rules which govern the regiochemical and stereochemical outcome of 5-exo carbon radical cyclisations are well known[5-8] the study of the stereochemical outcome of amidyl radical cyclisations has received much less attention, (**Scheme 1**).[9] The stereochemical outcome of cyclisation of carbon radicals can normally be predicted by application of the Beckwith model, which predicts that cyclisation preferentially takes place *via* a chair-like transition state with the substituent (R) in a pseudo-equatorial position, (**Fig. 1**).[5-8] As part of a programme developing routes to biologically active heterocycles we have examined the cyclisation of a number of amidyl radicals of type **(1)** in order to determine if the Beckwith rules also governed the outcome of amidyl radical cyclisations, (**Scheme 1**). We chose initially to investigate the stereoselectivity of "acyl mode" cyclisation reactions as these have been shown to take place much faster than the related "alkyl mode" amidyl radical cyclisations. We were particularly interested to determine how the nature of the nitrogen substituent (R^2) affected the stereochemical outcome of the cyclisations.

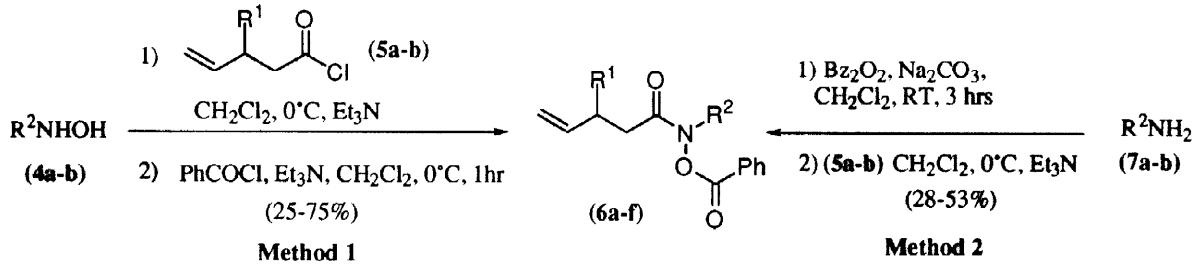


(1) **Scheme 1** (2) (3)

Fig. 1

PII: S0040-4039(98)01189-7

Synthesis of cyclisation precursors



Scheme 2

We recently described the synthesis of β-lactams via a 4-exo radical cyclisation approach[10] utilising *O*-benzoyl hydroxamic acid derivatives[11] as precursors for the desired amidyl radicals. Consequently, we prepared a range of 3-methyl and 3-phenyl-substituted *O*-benzoyl hydroxamic acid derivatives (**6a-f**) and examined the diastereoselectivity of their cyclisation reactions. The cyclisation precursors were prepared either by a two step sequence involving selective *N*-acylation followed by *O*-acylation of the corresponding *N*-alkylhydroxylamine salts (**4a-b**), (Method 1, **Scheme 2**), or by a one step process from either butylamine (**7a**) or i-propylamine (**7b**) using the procedure of Zinner[12] (Method 2, **Scheme 2**). The nitrogen substituents were chosen so as to probe the effect of a small (Me), removable (Bn), and bulky (*i*-Pr) group upon the outcome of the cyclisation.

R^1	R^2	(6)	Yield of (6) [a]	Method
Me	Me	(6a)	27%[b]	1
Me	Bn	(6b)	50%	1
Me	Bu	(6c)	53%	2
Me	*i*Pr	(6d)	28%	2
Ph	Me	(6e)	75%	1
Ph	Bu	(6f)	50%	2

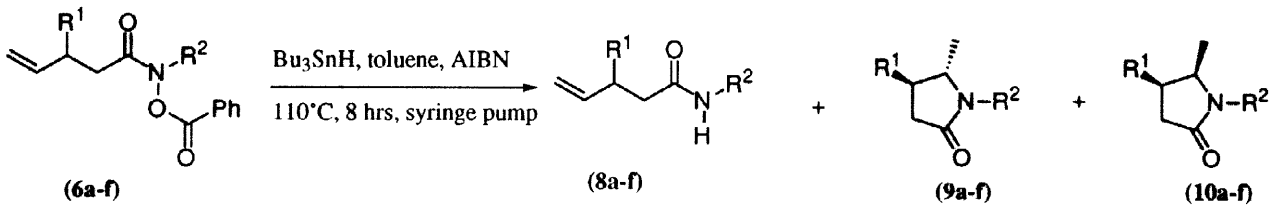
Table 1
Preparation of cyclisation precursors (**6a-f**)

[a]Represents combined yield for both steps
[b]Low yield due to water solubility of intermediate hydroxamic acid.

Cyclisation reactions

With the desired precursors (**6a-f**) in hand attention was turned to their cyclisation reactions. It was hoped that the steric nature of the nitrogen substituent (R^2) might play a role in determining the stereochemical outcome of the cyclisations. Hence, to a 0.15mmol/ml solution of the substrate in toluene was added, *via* a syringe pump over 8 hrs, Bu_3SnH (1.1eq) and AIBN (10mol%) (the final concentration of substrate was 0.075mmol/ml). After work-up and chromatography the cyclised diastereomeric compounds (**9**) and (**10**) were

isolated in addition to varying amounts of the reduced compound (**8**) (ratios of products were determined from the 400MHz ^{1}H NMR spectra of the crude samples, see Table 2). As all the reactions were carried out under identical conditions of concentration and temperature direct comparisons between the ratios of products can be made. In all cases the major cyclised products were assigned as having the *trans* configuration on the basis of either nOe measurements or by comparison to authentic samples.[13-14]



(6a-f) (8a-f) (9a-f) (10a-f)

Scheme 3

(6)	R^1	R^2	Cyclised/reduced	Yield[a] of (9) + (10)	d.e[b]
(6a)	Me	Me	17:1	47%	17%
(6b)	Me	Bn	12:1	53%	23%
(6c)	Me	Bu	c	55%	10%
(6d)	Me	*i*Pr	7.4:1	42%	11%
(6e)	Ph	Me	3.5:1	22%	43%
(6f)	Ph	Bu	12:1	82%	35%

Table 2

Results of cyclisation reactions

[a]Yield of isolated mixture of diastereomers

[b]D.e determined by NMR of crude material

[c]Negligable amount of reduced compound (8) detected in the crude NMR

In all the reactions the major products (**9a-f**) and (**10a-f**) arose from cyclisation with reduced products (**8a-f**) being formed in minor quantities. The results indicate that the steric nature of the nitrogen substituent does have a controlling effect on the level of reduced products formed. In the methyl-pendant series (**6a-d**) (R^1=Me) the precursors containing the more sterically demanding *N*-alkyl groups (benzyl (**6b**) and *i*-propyl (**6d**)) furnish the greatest amounts of reduced products. This is presumably due to the increased bulk at nitrogen which retards the relative rates of these respective cyclisations. On the other hand the steric nature of the nitrogen substituent seems to have little controlling effect on the diastereoselectivity of the cyclisation reactions. Although the major products (**9a-f**) were those predicted by the Beckwith rule, the diastereoselectivity exhibited was poor (far worse than reported for related carbon radical cyclisations[5-7] and aminyl radical cyclisations).[15] When bulkier pendant substituents (e.g. R^1 = Ph) were utilised the diastereoselectivity was found to increase, however only modestly. One possible explanation for the low stereoselectivity reported may be that the sp_2 nature of the amide carbonyl leads to a flattening of the conventional competing Beckwith "chair-like" transition states (Fig. A Vs Fig. B) or a lowering of the energy of any respective "boat-like" transition states. In order to propose a more

realistic model for the observed stereoselectivity it will be necessary to determine the electronic configuration of the amide radical. While it is generally accepted that the ground state electronic configuration of an amidyl radical is that of a Π_N radical, reactions thought to proceed via the higher energy Σ_N state as well as twisted Π_N states have been reported.[16-19] Molecular modelling studies are currently underway to try and rationalise the observed selectivity and these will be reported in due course.

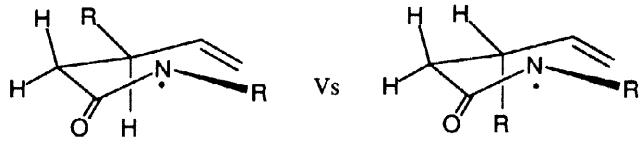


Fig. A Fig. B

Acknowledgements: We would like to acknowledge the EPSRC for a studentship (JLP) and the EPSRC mass spectrometry service at Swansea. In addition we would like to thank Dr. R. Bowman for helpful discussions.

1. Fossey, J.; Lefort, D.; Sorba, J. *Free Radicals in Organic Synthesis.* Chichester: Wiley, **1995.**
2. Clark, A.J.; Taylor, P.C. *Comprehensive Functional Group Transformations.* Vol 1 Oxford: Pergamon Press, **1995**, 319-377
3. Curran, D.P. *Comprehensive Organic Synthesis*, Oxford: Pergamon Press, **1991**, Vol 4, 716-779.
4. Curran, D.P. *Synthesis*, **1988**, 417
5. Beckwith, A.L.J.; Schiesser, C.H. *Tetrahedron.* **1985**, *45*, 3925
6. Beckwith, A.L.J.; Easton, C.J.; Lawrence, T.; Serelis, A.K. *Aust. J. Chem.* **1983**, 545
7. Beckwith, A.L.J.; Phillipou, G.; Serelis, A.K. *Tetrahedron Lett.* **1981**, *22*, 2811
8. Spellmeyer, D.C.; Houk, K.N. *J. Org. Chem.* **1987**, *52*, 959
9. For a review on nitrogen centered radicals see Esker, J.L.; Newcomb, M. *Advances in Heterocyclic Chemistry.* **1993**, *58*, 1
10. Clark, A.J.; Peacock, J.L. *Tetrahedron Letts.* **1998**, *39*, 1265
11. Boivin, J.; Callier-Dublanchet, A-C.; Quiclet-Sine, B.; Schiano, A.M.; Zard, S.Z. *Tetrahedron.* **1995**, *51*, 6517
12. Psiorz, M.; Zinner, G. *Synthesis.* **1984**, 217
13. Takahata, H.; Takamatsu, T.; Yamazaki, T. *J. Org. Chem.* **1989**, *54*, 4812
14. Sato, T.; Chono, N.; Ishibashi, H.; Ikeda, M. *J. Chem. Soc. Perkin Trans 1.* **1995**, 1115
15. Newcomb, M.; Marquardt, D.J.; Deeb, T.M. *Tetrahedron,* **1990**, *46*, 2329.
16. Lessard, J.; Griller, D.; Ingold, K.U. *J. Am. Chem. Soc.* **1980**, *102*, 3262
17. Sutcliffe, R.; Griller, D.; Lessard, J.; Ingold, K.U. *J. Am. Chem. Soc.* **1981**, *103*, 624
18. Mackiewicz, P.; Furtosse, R.; Waegell, B.; Cote, R.; Lessard, J. *J. Org. Chem.* **1978**, *43*, 3746
19. Glover, S.A.; Goosen, A,.; McCleland, C.W.; Schoonraad, J.L. *J. Chem. Soc. Chem. Commun.* **1986**, 645