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Anti-Beckwith stereoselectivity in amidyl radical cyclisations: Bu_3SnH-mediated 5-*exo-trig* acyl mode cyclisation of 2-substituted pent-4-enamide radicals

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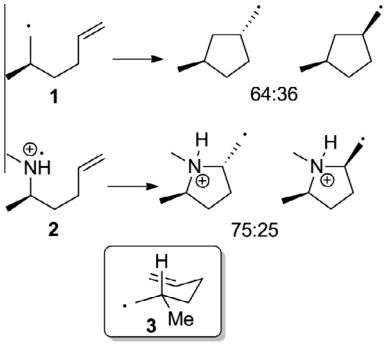
ABSTRACT

2-Substituted amidyl radicals derived from **8a–d** and **9a–d** undergo acyl mode 5-*exo-trig* cyclisation to give 3,5-*trans* pyrrolidinones **11a–d** and **14a–d** as the major products in low diastereoselectivity (de = 9–36%). The steric nature of the nitrogen substituent attached to the amidyl radical does not have a significant effect on selectivity. The stereochemical outcome is opposite to that expected based upon applying the Beckwith rule.

The rules governing the stereochemical outcome of 5-*exo* carbon radical cyclisations are well known[1–4] but the analogous nitrogen-centred radical cyclisations have been less well investigated.[5–8] The stereochemical outcome of hex-5-enyl radical **1** cyclisations can normally be predicted by application of the Beckwith–Houk model,[1–4] which predicts that cyclisation preferentially takes place via a chair-like transition state **3** with the substituent preferring a *pseudo* equatorial position. Thus, 1- and 3-substituted hex-5-enyl radicals afford mainly *cis*-disubstituted products, whereas 2- or 4-substituted species give mainly *trans* products (Scheme 1).[1–4]

Investigations into the stereochemistry of *5-exo-trig* aminyl and aminium cation radical **2** cyclisations have also been reported.[6] Bowman looked at the stereoselectivity of cyclisations of aminyl radicals derived from sulfenamides[7,8] while Newcomb investigated the cyclisation of cation radical **2** produced from the corresponding *N*-hydroxy pyridine-2-thione (PTOC) carbamate, which gave *trans* and *cis* pyrrolidines in a ratio of 3:1 at 25 °C (Scheme 1).[6] The cyclisation of related amidyl radicals has received less attention with only a few applications of their use in target synthesis.[5,9] Amidyl radicals can undergo cyclisation via two possible 'modes': cyclisation onto the alkyl side-chain (e.g., **4**) and onto the acyl side chain (e.g., **5**) (Scheme 2).

Cyclisation in the alkyl mode **4** occurs with similar stereoselectivity to aminyl radical cations,[10] but cyclisation in the acyl mode **5** (R = Me) gives poorer selectivity with 3-substituted systems.[11] Recent calculations at the UB3LYP/6-31+G(d,p) level have indicated that 5-*exo* chair-like (+5.3 kcal/mol) and 5-*exo* boat-like (+5.6 kcal/mol) transition states are very similar in energy for the cyclisation of unsubstituted pent-4-enamidyl radicals in the acyl mode,[12] and this may be partly responsible for the poor selectivities observed. For cyclisations of **5** the nature of the nitrogen substituent had little effect on the stereochemical outcome of the reaction,[11] which could be predicted via the Beckwith–Houk model, but more hindered groups (R = ^{i}Pr) led to slow cyclisations, in line with modelling predictions.[12] Recently, the stereochemical outcome of 6-*exo-trig* cyclisations of amidyl radicals has been



Scheme 1. Stereochemistry of cyclisations.

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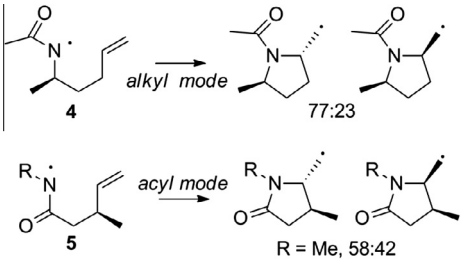
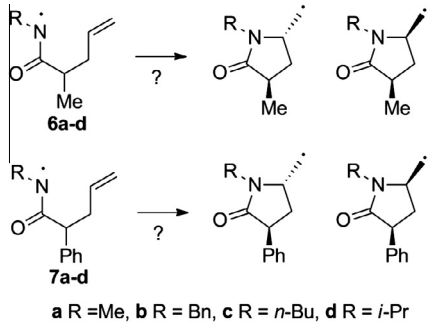


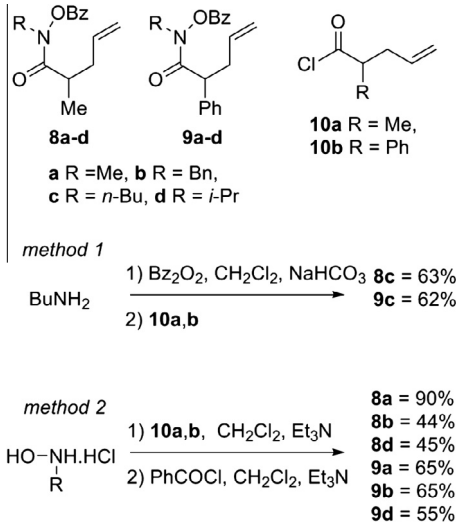
Scheme 2. Cyclisation modes of amidyl radicals

studied extensively both experimentally and theoretically.[13] However, while the regiochemical and stereochemical outcome of 5-*exo*-*trig* cyclisation of 3-,[11] 4- and 5-[13] substituted amidyl radicals in the acyl mode has been reported, the outcome of cyclisation of 2-substituted amidyl radicals has not. In this Letter we provide data to complete this series of stereochemical studies. Application of the Beckwith model would predict *cis* diastereomers should be the major products, but we anticipated that the diastereoselectivity of cyclisation would be poor, as observed for 4-substituted analogues **5** (Scheme 3).

The hydroxamic acid derivatives **8a**–**d** and **9a**–**d** were prepared by one of two methods (Scheme 4). The first method was based on the procedures of Zinner[14] and involved a two-step, one-pot reaction starting from the corresponding amine. The second procedure utilised a two-step approach involving initial selective N-acylation of commercially available hydroxylamine hydrochlorides with the appropriate acid chlorides **10a**,**b**, followed by *O*-benzoylation of



Scheme 3. An amidyl radical cyclisation approach to 3,5-disubstituted γ-lactams.



Scheme 4. Synthesis of amidyl radical precursors **8** and **9**.

the resulting hydroxamic acids (Scheme 4). The yields are combined yields for both of these steps. The cyclisations[15] were conducted by slow addition (syringe pump over 8 h) of a solution of tributyltin hydride (1.0 equiv) and AIBN (0.1 equiv) in toluene, to a refluxing solution of the precursor in toluene or in a 1/1 v/v mixture of toluene and cyclohexane. In each reaction the initial concentration of precursor in the solvent was between 0.08 and 0.16 mmol/ml. The tin hydride and AIBN were added in an equivalent amount of solvent thereby doubling the initial volume. After refluxing for a further 12 h, if analysis by TLC showed the reactions to not be fully complete an additional amount of tributyltin hydride (1.0 equiv) and AIBN (0.1 equiv) were added over another 8 h.

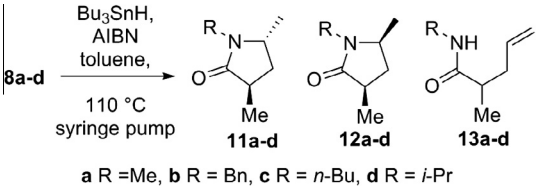
Purification of the crude mixtures was often difficult. The majority of the tin residues were removed by partitioning the crude product mixtures between, firstly, acetonitrile and hexane, and secondly, between acetonitrile and cyclohexane. Flash chromatography was used to purify the mixtures further. Generally, the diastereoisomers could not be separated fully, but in some cases, a pure sample of the major isomer could be obtained. The diastereomeric ratio was determined from either the 250 MHz ^{1}H NMR spectrum of the crude mixture directly after removal of the toluene solvent in vacuo, or after the first partitioning between acetonitrile and hexane. After this partition both the layers were carefully examined by ^{1}H NMR spectroscopy to determine whether any compounds were being extracted selectively. Diastereomers **11–12** and reduced products **13** were only found in the acetonitrile layer indicating that the diastereomeric ratio determined for this layer was representative of that of the reaction (Table 1).

Identification of the major isomers was accomplished from nOe difference spectra and by chemical correlation. Thus nOe could be used to assign unambiguously the stereochemistry of the major isomer of the cyclisation of **8b** (major isomer = **11b**). Analysis indicated a *trans* relationship for the major diastereomer (Scheme 5). The lactam **21a** had been reported by Armstrong[16] and thus offered a potential handle to check the stereochemistry of the products via chemical correlation. Hence, *S*-2-pyrolidinone-5-carboxylic acid was esterified using methanol to give the ester **17** in quantitative yield. Reduction of the ester to the alcohol followed by simultaneous protection of the NH and OH groups with benzaldehyde furnished the bicyclic lactam **18** in 47% yield for both steps. Deprotonation using LDA and methylation with methyl iodide gave a 3:1 ratio of the known diastereomers **19a**,**b** which could be separated by careful chromatography. Each of these diastereomers was then

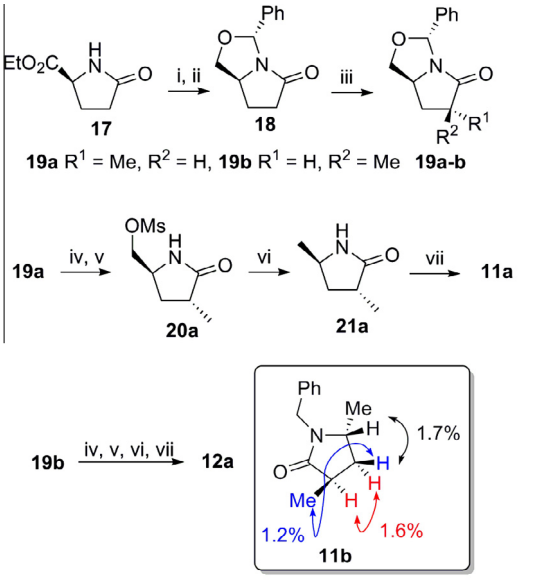
Table 1
Products from reactions of **8a**–**d** with Bu_3SnH

Substrate	Cyclised:reduced (**11**+**12**):**13**[a]	de[b] (%)	Yield (**11**+**12**) (%)
8a	9.0:1.0	11[16]	64
8b	–[d]	10	90
8c	2.3:1.0	12[c]	40
8d	2.3:1.0	9[c]	47

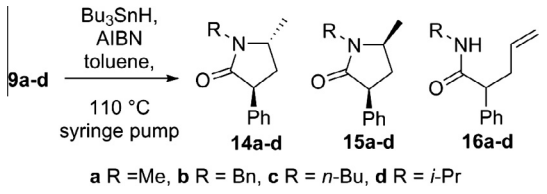
[a] Determined from the crude ^{1}H NMR spectrum (250 MHz).
[b] Major product **11**.
[c] Determined by GC.
[d] No **13c** detected.



Scheme 5. Cyclisation of precursors **8a**–**d**.



Scheme 6. Determination of the stereochemistry of **11a**,**b**.



Scheme 7. Cyclisation of precursors **9a**–**d**.

Table 2
Products from reactions of **9a**–**d** with Bu_3SnH

Substrate	Cyclised:reduced (**14**+**15**):**16**[a]	de[b] (%)	Yield (**14**+**15**) (%)
9a	9.0:1.0	25[18]	86
9b	16.0:1.0	25	73
9c	7.3:1.0	36	68
9d	9.0:1.0	36	52

[a] Determined from the crude ^{1}H NMR spectrum (250 MHz).
[b] Major product **14**.

separately subjected to toluenesulfonic acid deprotection, mesylation, iodide formation and reduction to give both the *cis* and *trans* **21a** derivatives. During the manipulation it was possible to crystallise and obtain an X-ray structure for the *trans* mesylate **20a** confirming the literature assignment of the stereochemistry. Methylation of both diastereomers of **21** using NaH and MeI furnished authentic samples of **11a** and **12a** which unambigously assigned the major products from cyclisation as being *trans* (Scheme 6).[17]

Using the same cyclisation protocol as before, we next turned our attention to the cyclisation of the 2-phenyl **9a–d** substituted precursors (Scheme 7). Determining the stereochemistry of the major isomer of the 3-phenyl substituted series **14** was more problematic (Table 2). NOe experiments were not conclusive, (due to overlap of signals) and no authentic samples had been reported in the literature at the time of publication. However, we have assigned tentatively the major isomers as *trans* **14** based upon two pieces of literature precedence. Firstly, Ollis and Stoddart[18] published a thorough analysis of the stereochemical assignment of related 3,5-disubstituted-γ-butyrolactones **22a,b** in which they were able to correlate the shift of the H-3 proton and the relative difference of the chemical shift of the α- and β-H-4 protons with stereochemical assignment based upon authentic samples (Fig. 1). Thus, the $\Delta\delta$ between the α- and β-protons at C-4 is generally larger for *cis* butyrolactones **22a** ($\Delta\delta$ = 0.75) than *trans* derivatives **22b** ($\Delta\delta$ = 0.28) and the H-3 proton is more deshielded for *trans* derivatives (3.90 ppm) relative to *cis* compounds (3.85 ppm). We can now extend this analysis to γ-lactams because the same phenomena were observed for all of the unambiguously assigned 3-methyl substituted γ-lactams **11a–d** and **12a–d** (e.g., *trans* **11b** $\Delta\delta$ = 0.09, *cis* **12b** $\Delta\delta$ = 1.20).

Applying the same criteria to the 3-phenyl series **14a–d** and **15a–d** indicates that the major products are also *trans*.[19] The second piece of evidence for the proposed assignment is that replacing the pendant methyl group with a phenyl group in the cyclisation of **5** and **23** (Scheme 8), did not change the sense of the major diastereomer.[11] Indeed moving from a methyl group to a phenyl group **5**→**23** increased the de by ~20%. This correlates with the similar observation made with the γ-lactam series **8**→**9** (15–26% increase).

The results obtained indicate that the nature of the nitrogen substituent had little or no effect on the diastereoselectivity in the cyclisations of **8a–d**, and only a minor effect in the cyclisations of **9a–d**. It was found that the larger pendant substituents (Me vs Ph) provide higher selectivity upon cyclisation. A similar conclusion was reached in the study of **5** and **23**. The major isomer in all cases arising from cyclisation of **8a–d** and **9a–d** was found to be the *trans* isomer (determined by nOe, chemical correlation and spectral correlation). This is contrary to that expected by application of the Beckwith rule. *trans*-Isomers were also reported as the major products in the cyclisation of **5** and **23** indicating that substitution at either the 2- or 3-positions leads to the same sense of diastereoselectivity.

Theoretical work indicates that for pent-4-enamide radicals the competing chair-like and boat-like transition states are close in

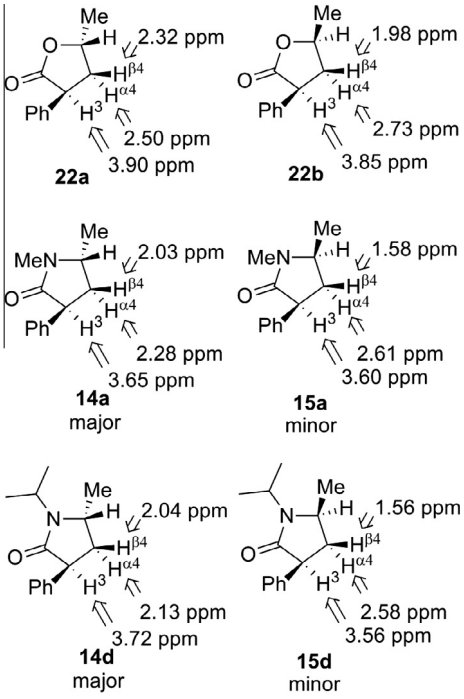
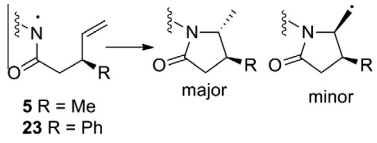


Figure 1. Stereochemical assignments of 3-phenyl-γ-lactams.



Scheme 8. Cyclisations of **5** and **23**.

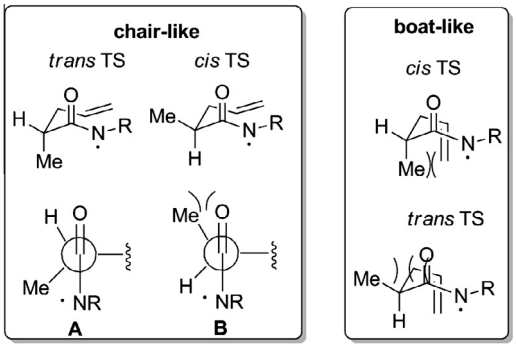


Figure 2. Possible transition states in the formation of the products.

energy, indicating that both should be considered in any analysis.[11] Examination of the Newman projections (Fig. 2), for the possible cyclisation of **8a–d** via chair-like TSs indicates a significant eclipsed interaction between the pendant methyl substituent and the carbonyl group in transition state **B** which is absent in transition state **A** where the methyl group adopts a pseudo axial position, thus favouring the observed *trans* isomers. Analysis of the boat-like TSs suggests that both have significant steric interactions indicating that these will be less important in stereochemical determination than the chair-like TS **A**, although modelling would have to be undertaken to confirm this.

In conclusion we have provided data that complete the set of stereochemical investigations for substituents attached to pent-4-enamide radicals. We have shown that the major *trans* isomers are not those predicted by application of the Beckwith–Houk rule. We have also extended the work of Ollis and Stoddart[18] on correlating ^{1}H NMR chemical shifts of *cis* and *trans* 3-phenyl-5-methyl γ-lactone diastereomers to 3-phenyl-5-methyl γ-lactams.

Acknowledgements

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17. *N-Methyl-3,5-dimethylpyrrolidin-2-one* (***11a***/***12a***). (Initial concentration of substrate 0.12 M); 2:1 hexane:EtOAc, 64% as an inseparable mixture of diastereoisomers (ratio 54.5:45.5, *trans:cis*); IR ($CDCl_3$)/cm^{-1} (mixture) 2966, 1674, 1456; ^{1}H NMR (400 MHz; $CDCl_3$) discernible data for the *trans* isomer: 1.15 (3H, d, J = 7.3 Hz), 1.17 (3H, d, J = 6.3 Hz), 1.75 (2H, m), 2.49 (1H, m), 2.78 (3H, s), 3.48 (1H, m); discernible data for the *cis* isomer: 1.18 (3H, d, J = 7.0 Hz), 1.20 (3H, d, J = 6.3 Hz), 1.18–1.20 (1H, m), 2.32–2.43 (2H, m), 2.77 (3H, s), 3.39 (1H, m); ^{13}C NMR (100 MHz; $CDCl_3$) (mixture) 16.5, 16.7, 19.1, 20.3, 27.3, 27.5, 35.2, 35.3, 36.5, 36.6, 53.4, 53.6, 177.1, 177.5; *m*/*z* (EI) 127 (M^+, 43%), 112 (100), 105 (87). HRMS calculated for $C_7H_{14}NO$: 128.1075, found 128.1063.
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19. *N-Methyl-5-methyl-3-phenylpyrrolidin-2-one* (***14a***/***15a***). (Initial concentration of substrate 0.1 M); 2:1 hexane:EtOAc, 86% as a partially separable mixture of diastereoisomers (ratio 62.5:37.5, *trans:cis*); IR (mixture) ($CDCl_3$)/cm^{-1} 2967, 1686, 1451; ^{1}H NMR (250 MHz; $CDCl_3$) discernible data for the *trans* isomer: δ 1.26 (3H, d, J = 6.1 Hz), 2.03 (1H, m), 2.28 (1H, m), 2.88 (3H, s), 3.65 (2H, m) 7.19 (5H, m); discernible data for the *cis* isomer: δ 1.30 (3H, t, J = 6.1 Hz), 1.58 (1H, m), 2.61 (1H, m), 3.53 (1H, m), 3.60 (1H, t, J = 10.1 Hz), 7.20 (5H, m); ^{13}C NMR (90 MHz; $CDCl_3$) discernible data for the *trans* isomer: 19.2, 27.7, 36.2, 47.0, 54.0, 126.9, 128.0 (×2), 128.7 (×2), 140.0, 174.7; discernible data for the *cis* isomer: 20.3, 27.7, 37.5, 48.3, 53.5, 126.9, 128.4 (×2), 128.7 (×2), 139.8, 175.1; *m*/*z* (EI) (mixture) 189 (M^+, 91%), 117 (100), 174 (93). HRMS calculated for $C_{12}H_{15}NO$: 189.1154, found 189.1150.