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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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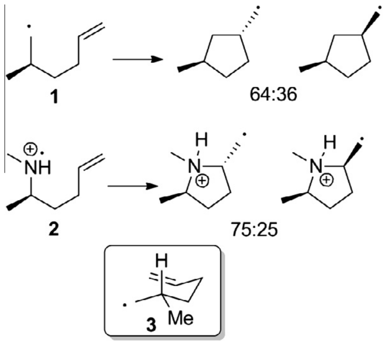
ABSTRACT

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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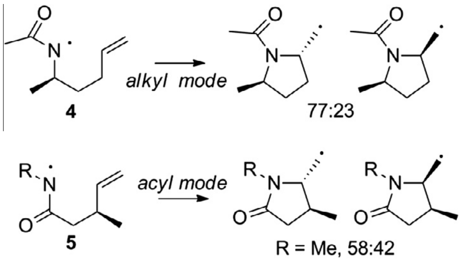
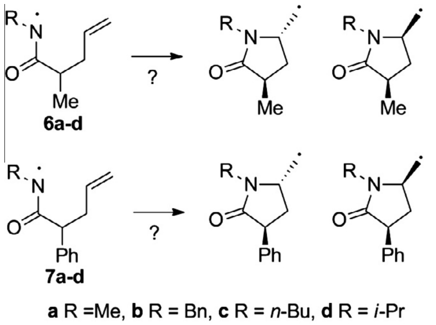


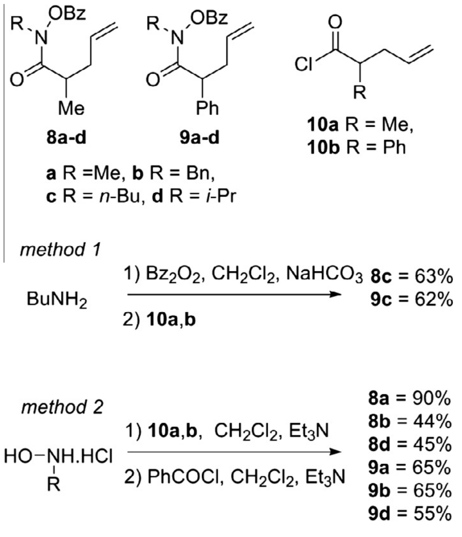
Scheme 2. Cyclisation modes of amidyl radicals

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 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.



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



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

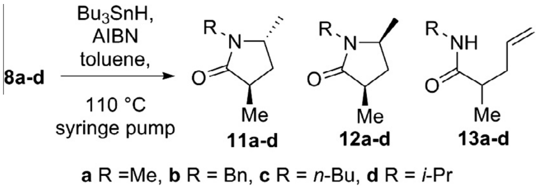
Purification of the crude mixtures was often difficult. The majority of the tin residues were removed by partitioning the crude product mixtures between, firstly, acetonitrile and hexane, and secondly, between acetonitrile and cyclohexane. Flash chromatography was used to purify the mixtures further. 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**.