Stereoselectivity in Amidyl Radical Cyclisations: Alkyl Mode Cyclisations

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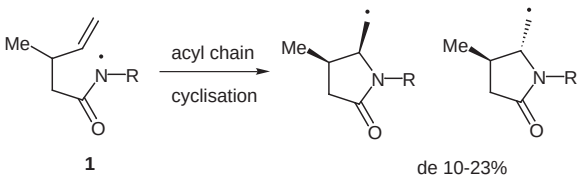
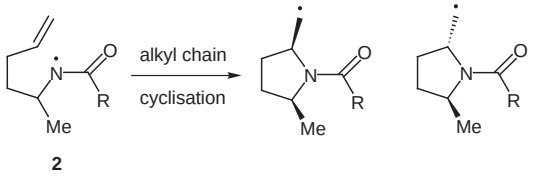
Abstract: Amidyl radicals **2** generated from tributylstannane mediated homolysis of O-benzoyl hydroxamic acid derivatives **6a-g** undergo alkyl mode 5-*exo* cyclisation to give mixtures of *cis* and *trans* N-acyl pyrrolidinones (d.e. = 54-74%). The efficiency of the process was found to be dependant upon the steric and electronic nature of the nitrogen substituent.

Key words: amidyl radicals, cyclisation, stereochemistry, hydroxamic acid derivatives, 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 1-2)[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 chain substituent preferring a pseudo-equatorial position[5-8]. As part of a programme developing routes to biologically active heterocycles we have examined the cyclisation of a number of amidyl radicals in order to determine if the Beckwith rules also govern the outcome of amidyl radical cyclisations. We recently reported the stereochemical outcome of the cyclisation of amidyl radicals of type **1** to give N-alkyl pyrrolidinones (Scheme 1)[10]. These cyclisations were found to proceed with poor diastereoselectivities (d.e = 10-23%) presumably due to the presence of the amide carbonyl group which led to a flattening of the conventional chair-like transition state during cyclisation. We now wish to report the outcome of the cyclisation reactions of the related amidyl radicals **2** in which the amide carbonyl group is situated outside the ring after cyclisation. We were particularly interested to determine if the steric and electronic nature of the nitrogen substituent (R) affected the stereochemical outcome of the cyclisations.

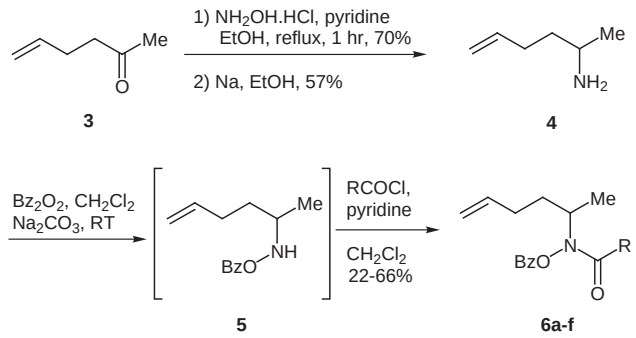


Scheme 1



Scheme 2

Both Zard[11] and ourselves[10,12] have previously reported the use of O-benzoyl-N-alkyl hydroxamic acid derivatives as precursors to amidyl radicals. Consequently, we prepared a range of derivatives **6a-f** in which the N-acyl substituent was systematically changed both sterically and electronically. The cyclisation precursors were readily prepared from 5-hexen-2-one **3** by initial reaction with hydroxylamine hydrochloride and pyridine to furnish the corresponding oxime (70%)[13] followed by reduction with Na/EtOH to give the amine **4** (57%). Reaction of **4** with Bz_2O_2 and sodium carbonate formed the O-benzoylated hydroxylamine **5** which was acylated *in situ* to furnish the cyclisation precursors **6a-f**[14].

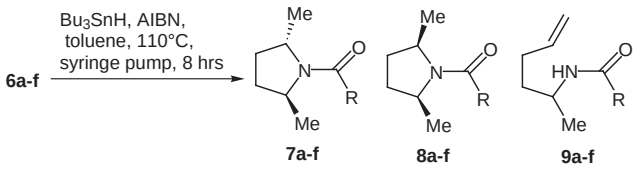


Scheme 3

Table 1. Preparation of cyclisation precursors 6a-f

6	R	Yield
6a	Me	66%
6b	*s*-Bu	40%
6c	*t*-Bu	56%
6d	*i*-Pr	56%
6e	Bn	22%
6f	OMe	56%

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) 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 **7a-f** and **8a-f** were isolated in addition to varying ratios of the reduced compound **9a-f** (ratio of products were determined from the 250 MHz or 400 MHz ^{1}H NMR spectrum of the crude samples).



Scheme 4

Although conversions were good and NMR yields of the cyclised products were high (60-70%) the isolated yields of the cyclised products after chromatography were low (**7a/8a** = 38%, **7e/8e** = 52%[15], **7f/8f** = 46%). This was a consequence of the repeated chromatography required to remove the final traces of tin residues from the mixtures[16]. In addition to the cyclised and reduced compounds **7-9e** produced in the cyclisation of **6e** a trace amount (3%) of a further product **10** was detected as a 1/1 mixture of diastereomers. The formation of **10** may arise via a hetero [3,3] sigmatropic rearrangment of the enol form of the starting material **6e** (see Fig. 1)[17].

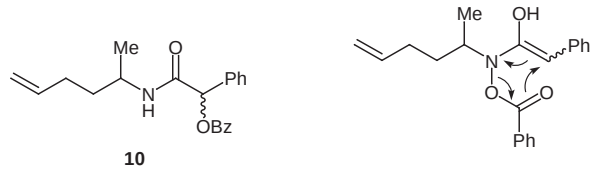
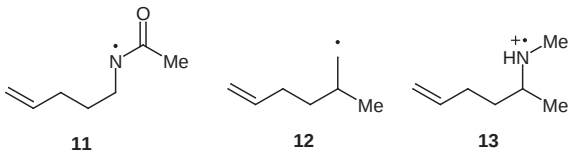


Figure 1

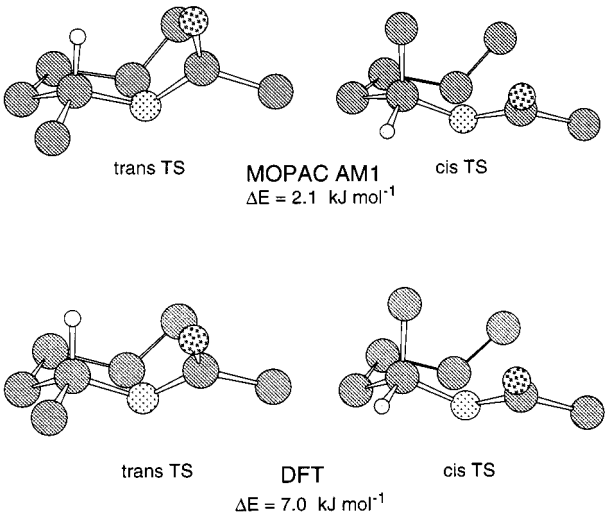
The cyclisation reactions failed with a bulky (2° or 3° alkyl) N-substituted group with either reduction products **9b,d** or unreacted starting material **6c** being isolated. These results are consistent with the large amounts of reduction products reported with bulky alkyl N-substituents in the related acyl mode amidyl radical cyclisations e.g of **1**[10]. This is presumably due to the increased steric bulk at nitrogen which retards the relative rates of these respective cyclisations allowing for competitive trapping by Bu_3SnH prior to cyclisation. The major cyclised diastereomers **7a** and **7f** were determined to be *trans* by comparison of their spectroscopic data with authentic samples of *cis* and *trans* products[18]. The ^{13}C NMR methyl resonances in the *cis* isomers appear further downfield than those of the corresponding *trans* isomers. The previously unknown major compound **7e** was also assigned as *trans* based upon this effect and by comparison of an authentic sample prepared by acylation of a commercially available 2:1 *cis:trans* mixture of 2,5-dimethyl pyrrolidine (Aldrich)[19].

The formation of the *trans* compounds as the major products is in line with the well established "Beckwith Model" suggesting that cyclisation proceeds *via* a chair-like transition state. Semi-empirical MO calculations using the AM1[20] approximation, as implemented in version 6 of MOPAC[21] indicated that for the unsubstituted radical **11** the chair-like transition state was lower in energy than the boat-like transition state (ΔE = 2.5 kJ mol^{-1}). In addition both semi-empirical (AM1) and higher level ab initio calculations (DFT[22]) indicated that the transition state for cyclisation of **6a** to **7a** was lower in energy than that to **8a** (ΔE= 2.1 (AM1) and 7.0 kJ mol^{-1} (DFT) respectively). Interestingly the diastereoselectivity of the reactions are significantly better than for related amidyl radical cyclisations proceeding in the acyl mode (de = 10-23%)[10] and for the cyclisation of the 2-methyl-5-hexenyl carbon radical **12** (de=30%)[5-7] and the corresponding N-methyl-5-pentenaminium radical **13** (de=34%)[23]. The steric nature of the N-substituent of the amidyl radicals seems to have little controlling effect on the stereoselectivity of the process with both **6a** and **6e** undergoing cyclisation with similar selectivities (de 54% and 58% respectively). The slightly higher selectivity in the cyclisation of **6f** suggests that the electronic nature of the N-substituent may play an important role in controlling the outcome of the reaction, however how this electronic effect influences the stereoselectivity is less certain. Further experiments in combination with molecular modelling are currently underway to probe further the electronic influences of this process and will be reported at a later date.



References and notes

(1) Fossey, J.; Lefort, D.; Sorba, J.; *Free Radicals in Organic Synthesis*. Wiley: Chichester, **1995**.
(2) Curran, D.P.; *Comprehensive Organic Synthesis*, Pergamon Press: Oxford, **1991**, Vol 4, 716-779.
(3) Curran, D.P.; *Synthesis* **1988**, 417.
(4) Giese, B.; *Radicals in Organic Synthesis: Formation of Carbon-Carbon Bonds*, Pergamon Press, Oxford, **1986.**
(5) Beckwith, A.L.J.; Schiesser, CH. *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 Lett.* **1998,** 39, 6029.
(11) Boivin, J.; Callier-Dublanchet, A-C.; Quiclet-Sine, B.; Schiano, A.M.; Zard, S.Z. *Tetrahedron* **1995**, *51*, 6517.
(12) Clark, A J.; Peacock, J.L.; *Tetrahedron Lett.* **1998,** 39, 1265.
(13) Naegeli. *Chem Ber*. **1883**, 496.
(14) Psiorz, M.; Zinner, G.; *Synthesis* **1984**, 217.
(15) Yield 53% is given for an inseparable mixture of cyclised compounds **7e**, **8e** and reduced compound **9e**.
(16) The best approach to remove excess tin residues before chromatography was to partition the crude reaction mixture between cyclohexane and acetonitrile and then evaporate the acetonitrile layer to furnish purified cyclised materials.
(17) Al-Faiyz, Y.S.S.; Clark, A J.; Filik, R.P.; Peacock, J.L.; Thomas, G.H.; *Tetrahedron Lett.* **1998,** 39, 1269.
(18) Harding, K.E.; Burks, S.R.; *J. Org. Chem.* **1981**,46, 2011.
(19) Selected data for **7e**. IR 1636cm^{-1} (C=O) ^{1}H NMR (400MHz, $CDCl_3$) 4.25 (1H, quint, J=6.3Hz, CHN), 4.02 (1H, quint, J=6.7Hz, CHN), 3.69 (1H, d, J=15.1Hz, C*H*HPh), 3.62 (1H, d, J=15.1Hz, C*H*HPh), 2.17-2.03 (2H, m, 1H on C-3 and C-4), 1.7-1.5 (2H, m, 1H on C-3 and C-4), 1.18 (3H, d, J=6.3Hz, Me), 1.14 (3H, d, J=6.7Hz, Me); ^{13}C NMR (100MHz, $CDCl_3$) 169.5, 135.8, 128.7, 128.3, 126.4, 53.6, 53.0, 41.6, 30.7, 28.9, 21.7, 18.8
(20) Dewar, M.J.S.; Zoebisch, E.G.; Healy, E.F.; Stewart, J.J.P.; *J. Am. Chem. Soc.* **1985**, 107, 3902.
(21) Stewart, J.J.P.; MOPAC (QCPE 455).
(22) Density Functional Theory Calculations were performed using the Amsterdam Density Functional Program version 2.3[24]. Geometries were optimised at the Local Density Approximation level with energies computed using the Becke88/Perdew86[25,26] gradient corrections. Basis sets were STO triple-ζ + polarisation on all atoms.
(23) Newcomb, M.; Marquardt, D.J.; Deeb, T.M.; *Tetrahedron* **1990**, 46, 2329.
(24) ADF version 2.3.0, Theoretical Chemistry, Vrije Universiteit, Amsterdam, 1997.
(25) Becke, A.D.; *Phys. Rev. A* **1988**, 38, 3098
(26) Perdew, J.P.; *Phys. Rev. B.* **1986**, 33, 8822.