An Amidyl Radical Cyclisation Approach Towards the Synthesis of β-Lactams

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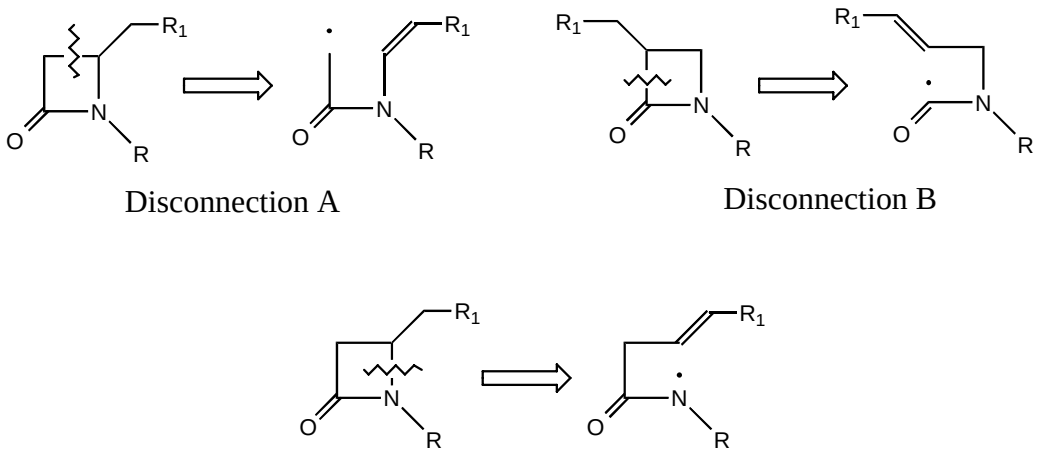
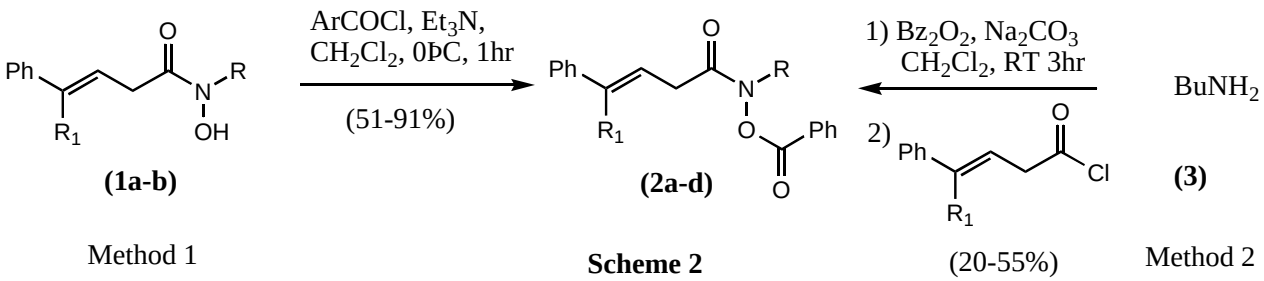
Abstract: Amidyl radicals generated from tributylstannane mediated homolysis of O-benzoyl hydroxamic acid derivatives **(2a-d)** undergo 4-exo trig cyclisation to furnish β-lactam derivatives **(4a-d).**

In recent years intramolecular radical additions to alkenes have been developed, and these represent a powerful tool for the construction of cyclic arrays. The success of radical mediated transformations in synthesis has in part been due to the neutral nature of the reactions, which allow a wide degree of functionality to be tolerated in substrates. The majority of published work has focused upon the reactions of carbon centered radicals[1], with the reactions of nitrogen substituted radicals receiving much less attention[2]. Cyclisation of aminyl radicals is often problematic due to their potential reversibility and in addition the nucleophilic nature of the radical often facilitates competitive trapping of the initial radical by tributylstannane. These problems can be overcome by using amidyl radicals instead of nucleophilic aminyl radicals. Recently, two new procedures for the generation of amidyl radicals have been reported. The use of N-acyl sulpheneamides as radical precursors has been reported by Newcomb[3], while the use of O-benzoyl hydroxamic acid derivatives has been explored by Zard[4]. Both groups have demonstrated that amidyl radicals undergo efficient 5-exo-trig cyclisation under neutral conditions. In addition tandem cyclisations are possible giving pyrrolizine-3-one systems. As part of an ongoing interest into the synthesis and chemistry of β-lactam containing compounds and 4-oxo-2-azetidineacetic acids we have investigated the outcome of 4-exo-trig cyclisations of amidyl radicals (disconnection C). Other groups have reported the formation of β-lactams by 4-exo radical cyclisations of carbon centered radicals (disconnections A and B)[5,6], however our approach is conceptually different and hence we wish to report in this letter our preliminary investigations in this area.



Scheme 1

Preparation of cyclisation precursors.

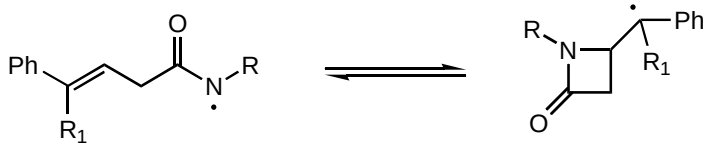


We chose to use the Zard procedure[4] for the generation of the desired amidyl radicals and consequently we prepared a number of O-benzoylhydroxamic acid derivatives **(2a-d)** as cyclisation precursors. These could be conveniently prepared utilising one of two procedures. Hence, treatment of N-alkyl-N-hydroxyphenyl-3-butenamides **(1a-b)** with one equivalent of triethylamine and benzoyl chloride at 0˚C furnished the desired cyclisation precursors **(2a-b)**, see Table 1. Alternatively, the cyclisation precursors **(2c-2d)** could be prepared in one pot by the reaction of butylamine **(3c)** with one equivalent of benzoyl peroxide in the presence of Na_2CO_3 in dichloromethane followed by the addition of the appropriate acid chloride. Although this furnished the desired precursors **(2c-2d)** a significant amount of N-butylbenzamide (15-25%) was also isolated. The competing formation of amides when primary amines (i.e. butylamine) are used in this reaction is well documented[7].

Compound	R	R_1	Method	Yield
(2a)	Me	H	1	91%
(2b)	Bn	H	1	51%
(2c)	Bu	H	2	53%
(2d)	Bu	Ph	2	55%

Table 1

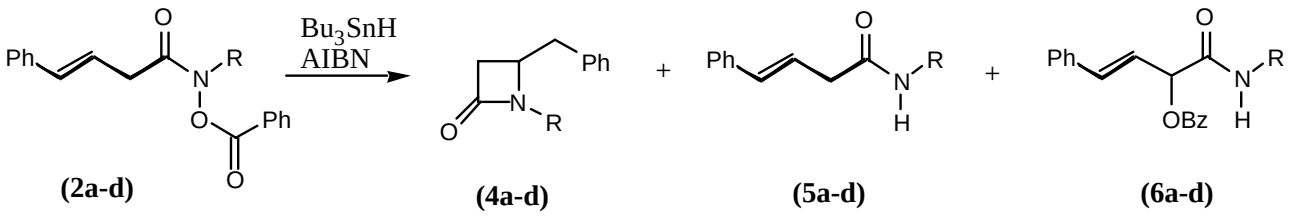
With the desired precursors **(2a-2d)** in hand attention was turned to their cyclisation reactions. We hypothesised that although the 4-exo-trig cyclisation would be reversible the presence of the phenyl substituent would lead after cyclisation to a stabilised benzylic system **(4)**, scheme 3. Reduction of this radical by Bu_3SnH would lead to the formation of the desired β-lactam systems **(4a-d)**.



Scheme 3 **(4)**

Results

A typical procedure is as follows: To a solution of the substrate (3mmol) in 1:1 cyclohexane:toluene (15ml, 0.2 mmol of substrate per ml) was added a solution of Bu_3SnH (3.3mmol) and AIBN (5mol%) in 1:1 cyclohexane:toluene (15ml) over 8 hours via a syringe pump. The solution was then refluxed overnight. Evaporation of the solvents and partitioning of the residue between acetonitrile and cyclohexane allowed separation of the tin byproducts (cyclohexane layer) from the desired products (acetonitrile layer). Further purification by column chromatography furnished the desired β-lactams, (see table 2)



(2a-d) **(4a-d)** **(5a-d)** **(6a-d)**

Scheme 4

Analysis of the reaction mixture from cyclisation of **(2a)** indicated that in addition to the desired β-lactam **(4a)** a similar amount of the corresponding reduction product **(5a)** and the rearranged product **(6a)** had formed (ratio of **(4a):(5a):(6a)** = 1.0:1.8:1.0 (70%), isolated yield of **(4a)**[8] = 15%) . Interestingly no product arising from 5-endo cyclisation was detected[8]. Whilst this initial result was discouraging in relation to the isolated yield of the desired β-lactam it showed for the first time that it was possible to facilitate 4-exo

amidyl radical cyclisations using Bu_3SnH mediated reactions of O-acyl hydroxamic acids. In order to determine if the nature of the groups attached to nitrogen or the addition of a second phenyl substitutent could effect the ratio of these three products, particularly the amount of reduction product, we next examined the cyclisation reactions of **(2b-d)**, table 2[9].

Compound[a]	Yield[b]	Ratio of 4:5:6[c]
(2a)	70% (15%)	1.0:1.8:1.0
(2b)[d]	82% (-[f])	3.0:1.0: -[e]
(2c)	68% (28%)	1.4:1.0:1.0
(2d)	59% (-[f])	2.2:1.0: -[g]

a) Initial concentration of substrate 0.2 mmol per ml.
b) Combined yield of (4), (5), and (6), isolated yield of (4) in brackets.
c) Ratio measured from crude NMR.
d) Initial concentration of substrate 0.15 mmol per ml.
e) a trace of (6) was detected by NMR.
f) (4) not separated from (5).
g) no (6) was detected

Table 2

The amount of cyclised product could be increased by either conducting the cyclisation at a slightly lower initial concentration **(2b)** (0.15 mmol per ml) or by adding a further stabilising substituent (R_1=Ph) to the alkene **(2d)**. It is noteworthy that in both cases little if any of the rearranged products were detected in the crude reaction mixture. Cyclisation of the N-butyl analogue **(2c)** gave similar results to the N-methyl analogue **(2a)** at similar initial starting concentrations. Attempts to cyclise **(2c)** using a higher initial concentration (2.0mmol per ml) lead to rearranged and reduction products **(6c)** and **(5c)** (ratio 1.3:1) respectively with only traces of cyclised product **(4c)** detected in the crude NMR. The formation of rearranged products **(6)** deserves comment. It is possible that these products may arise via a thermal [3,3]-sigmatropic rearrangent of the corresponding enol form of **(2)**[10]. This does not rule out however the possibility of some other mechanism in the above reactions. In conclusion we have demonstrated that 4-exo amidyl radical cyclisations to give β-lactams are possible albeit in low yields. It may be possible to optimise the yield of the cyclised products by utilising precursors which contain sulfur-substituent(s) at the vinylic bond in a similar way to that reported by Ishibashi and Ikeda[5]. The outcome of this work will be reported at a later date.

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9. **(4b)** : NMR ^{1}H (250MHz, $CDCl_3$) 4.60 (1H, d, J = 15.0Hz, NCH*H*Ph), 3.95 (1H, d, J = 15.0Hz, NC*H*HPh), 3.66 (1H, m, H-4), 2.93 (1H, dd, J = 14.6, 4.9Hz, H-3), 2.91 (1H, dd, J = 13.7, 5.7Hz, CH*H*Ph), 2.71 (1H, dd, J = 13.7, 7.6Hz, CH*H*Ph), 2.64 (1H, dd, J = 14.6, 2.4Hz, H-3).
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