# Tandem Cyclisations of Amidyl Radicals Derived from O-Acyl Hydroxamic Acid Derivatives

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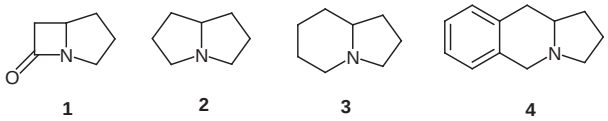
**Abstract:** Amidyl radicals generated from tributylstannane mediated homolysis of O-acyl hydroxamic acid derivatives **5a-b** undergo tandem cyclisations to give pyrrolizidinones **6a-c** and indolizidinones **7a-b** respectively while **5c-d** undergo monocyclisation to give β-lactam **10a** and γ-lactam **11a** respectively. On the other hand the reaction of **5d-f** with $Cu(OTf)_2$/DBN furnishes mixtures of reduction **10b**, monocyclisation **10a** and tandem cyclisation **9** products with the ratio dependant upon the nature of the O-acyl group and the solvent and concentration employed.

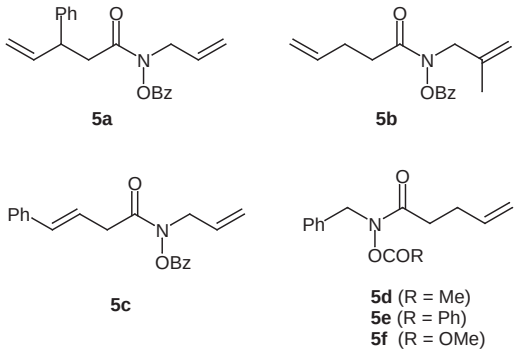
**Key words:** amidyl radicals, cyclisation, copper complexes, hydroxamic acid derivatives, tandem reactions

Biologically active nitrogen heterocycles occur widely in nature. In particular the bicyclic and tricyclic systems shown below **1-4** are prevalent in a number of naturally occurring compounds ranging from thienamycin[1], the pyrrolizidine[2], indolizidine[3] and the lycorane[4] family of alkaloids respectively. We have recently published the use of O-benzoyl N-alkyl hydroxamic acid derivatives as precursors for amidyl radicals[5] which can undergo 4-*exo* cyclisation[6], or 5-*exo* cyclisation[7-8] reactions to furnish β-lactams or pyrrolidinones respectively. We wish to report in this letter attempts to extend this methodology to furnish bicyclic and tricyclic frameworks related to **1-4**.



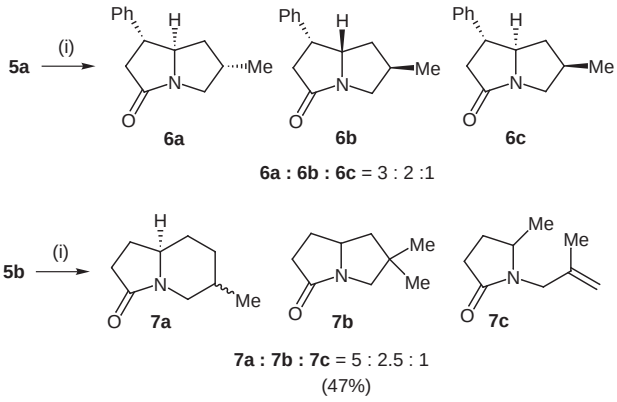
**1** **2** **3** **4**

The use of O-benzoyl hydroxamic acid derivatives as precursors to amidyl radicals was first reported by Zard[9]. In order to determine the scope of this methodology for the synthesis of more functionalised molecules we investigated the $Bu_3SnH$ mediated reactions of the precursors **5a-f**. These were prepared using our previously described methodology.[6-8, 10]



**5a** **5b** **5c**

**5d** (R = Me)
**5e** (R = Ph)
**5f** (R = OMe)



**6a** **6b** **6c**

**6a : 6b : 6c** = 3 : 2 :1

**7a** **7b** **7c**

**7a : 7b : 7c** = 5 : 2.5 : 1
(47%)

**Scheme 1** (i) syringe pump 6 hrs $Bu_3SnH$, AIBN,1:1 v:v $C_6H_{12}$:$MeC_6H_5$

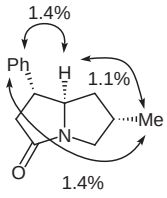


Fig 1

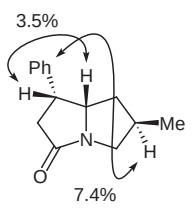


Fig 2

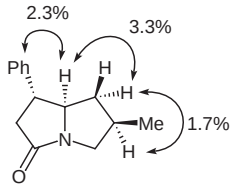


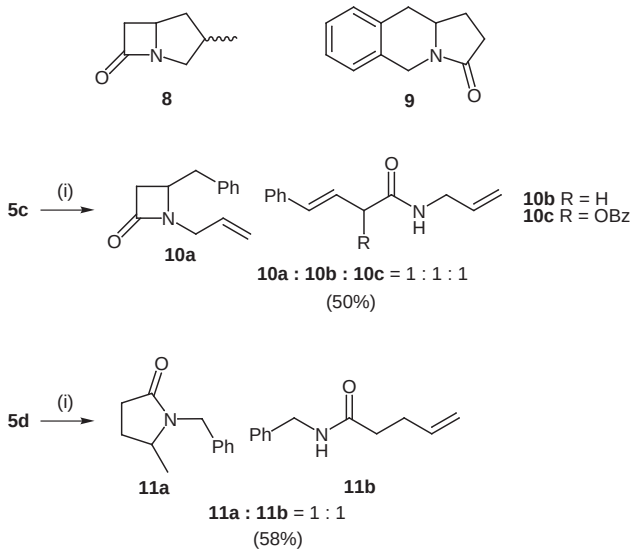
Fig 3

Reaction of both **5a-b** with 1.2 eq of $Bu_3SnH$/AIBN delivered by a syringe pump over 6 hours at reflux (initial concentration of substrate 0.2 mmol/ml) led to mixtures of the desired tandem cyclised products **6a-c** and **7a-b** respectively (Scheme 1). Cyclisation of **5a** furnished three diastereomeric pyrrolizidinones **6a-c** in a ratio of 3 : 2 : 1 respectively[11]. No reduction or monocyclisation products were detected. It proved difficult to remove all the last traces of tin residues from the products to obtain pure samples (after repetitive chromatography **6a** was isolated in 17% yield). The stereochemistry of each of the diastereomers was tentatively determined by nOe NMR experiments. The diastereoselectivity of the first cyclisation

(**6a+6c**:**6b** = 2:1) is similar to that reported for recent amidyl radical cyclisations[7] while that of the second would be expected to be similar to a 2-substituted hexenyl radical cyclisation. The Beckwith model[12] therefore predicts the observed formation of the all cis isomer **6a** as the major product.

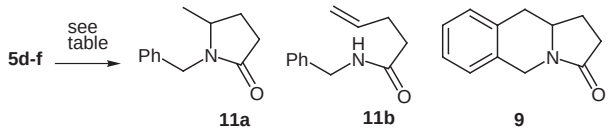
Cyclisation of **5b** under identical conditions produced a mixture of the indolizidinone **7a** and pyrrolizidinone **7b** in a 2:1 ratio (42%). In addition a small amount of the monocyclisation product **7c** (5%) was also isolated. The presence of the monocyclisation product is in line with a slower second cyclisation relative to **5a** caused by the steric hindrance now presented by the methyl alkene substituent[13].

Attempts to facilitate a tandem cyclisation of **5c** to give the bicyclo [2,3,0] system **8** found in thienamycin under identical conditions failed and the only cyclised product isolated was the monocyclised β-lactam **10a**. In addition to **10a** an equal amount of the reduction product **10b** and the rearranged product **10c** were isolated in a 50% overall yield. Attempts to prepare the tetrahydro-2H-pyrrolo-isoquinolinone skeleton **9** from **5d** via a tandem 5-*exo* amidyl radical cyclisation followed by a 6-*exo* carbon radical addition into the aromatic ring of the N-benzyl substituent also failed and only reduced **11b** and monocyclised **11a** products were isolated in 58% combined yield.




**Scheme 2** (i) syringe pump 6 hrs $Bu_3SnH$, AIBN,1:1 v:v $C_6H_{12}$:$MeC_6H_5$

Hypothesising that the failure of the latter tandem reaction was due to the reversibility of the second cyclisation into the aromatic ring (**12-13**) we investigated an alternative approach where the intermediate cyclohexadienyl radical **13** would be trapped irreversibly as a carbocation using added copper (II) salts[14], (Scheme 4). Successful conditions to facilitate the desired transformations involved using modified conditions to those reported for asymmetric Kharash reactions[15]. Hence when **5d-f** and $Cu(OTf)_2$/DBN in either acetone, acetonitrile or THF was heated at 120°C in a sealed tube for 48 hours varying ratios of **11a-b** and **9** were produced (Scheme 3, Table 1).



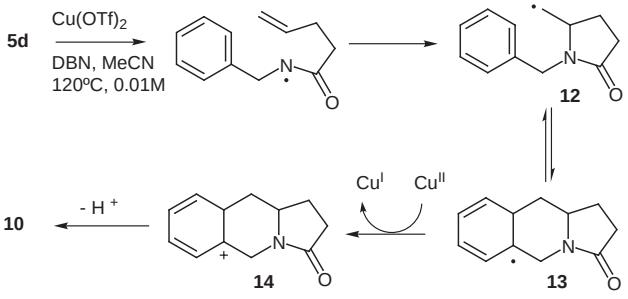

**Scheme 3**

The results clearly indicate that the nature of the O-acyl substituent is crucial for successful cyclisation reactions with **5d-e** giving a mixture of all three products (entries 1-2) while **5f** gave the reduction product **11b** only (entry 3). The nature of the solvent was also important in controlling the ratio of products (entries 4-5) but by far the most crucial factor in optimising the yield of the tandem product **9** was found to be concentration with best results at high dilution (entry 8).

**Table 1**

| Entry | 5 | Solvent | Conc | Yield[a] | Ratio[b] (**11a:11b:9**) |
|---|---|---|---|---|---|
| 1 | **5d** | MeCN | 0.19M | 84% (17%) | 4 : 76 : 20 |
| 2 | **5e** | MeCN | 0.19M | 91% (7%) | 6 : 86 : 8 |
| 3 | **5f** | MeCN | 0.19M | 77% (0%) | 0 : 100 : 0 |
| 4 | **5d** | THF | 0.19M | 85% (30%) | 18 : 44 : 38 |
| 5 | **5d** | acetone | 0.19M | 85% (23%) | 15 : 58 : 27 |
| 6 | **5d** | MeCN | 0.05M | 81% (28%) | 3 : 62 : 35 |
| 7 | **5d** | MeCN | 0.02M | 93% (38%) | 3 : 56 : 41 |
| *8* | ***5d*** | *MeCN* | *0.01M* | *93% (53%)* | *0 : 43 : 57* |

[a] Combined yield, with yield of **9** in brackets,
[b] Determined by 250 MHz $^1$H NMR




**Scheme 4**

The use of copper salts in oxidising radicals to cations is well established as is their use in catalysing the decomposition of the weak O-O bond of diacyl peroxides to give acyloxy radicals[16]. Due to the similarity in structure of N-

alkyl-O-acyl hydroxamic acid derivatives **5d-f** to diacyl peroxides a possible mechanistic rationale for the reaction sequence involves homolytic cleavage of the weak N-O bond in **5d-f** to furnish the desired amidyl radicals which then undergo tandem cyclisation to **13** followed by oxidation to **14** followed by elimination of a proton, (Scheme 4).

## References and Notes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