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Amidyl and Carbamyl Radicals by Stannane Mediated Cleavage of O-Benzoyl Hydroxamic Acid Derivatives.

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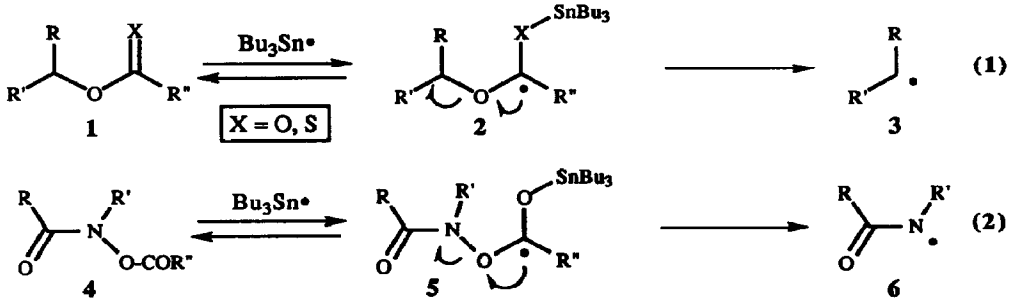
Abstract : O-Benzoyl hydroxamic acids react with tributylstannane in the presence of AIBN to give amidyl or carbamyl radicals which can be captured by an internal olefin.

As part of a general study of the reactivity and synthetic potential of nitrogen centered radicals and especially iminyls, we reported very recently that the cleavage of oxime benzoates with stannyl radicals represented a useful route to these species.[1] We now wish to describe preliminary results indicating that the same approach can also be usefully applied to the generation of amidyl radicals. Amidyl radicals have not been used extensively in synthesis, even though the scattered reports in the literature hint to a rich and interesting reactivity.[2] A lack of general, yet convenient and mild, methods for generating such intermediates appears to have hampered their development. Most of the earlier studies relied on N-haloamides which are relatively strong oxidising agents that are not always easily prepared and handled, especially in the context of complex or fragile molecules. In fact, the high reactivity of N-haloamides makes it difficult sometimes to dissociate their ionic from their radical chemistry. Very recent work, especially from the group of Newcomb,[3] has gone a long way in filling this gap in methodology as well as in providing some firm kinetic rate values so that the reactivity of amidyls can in a sense be predicted and compared to that of the much better known carbon centered radicals.

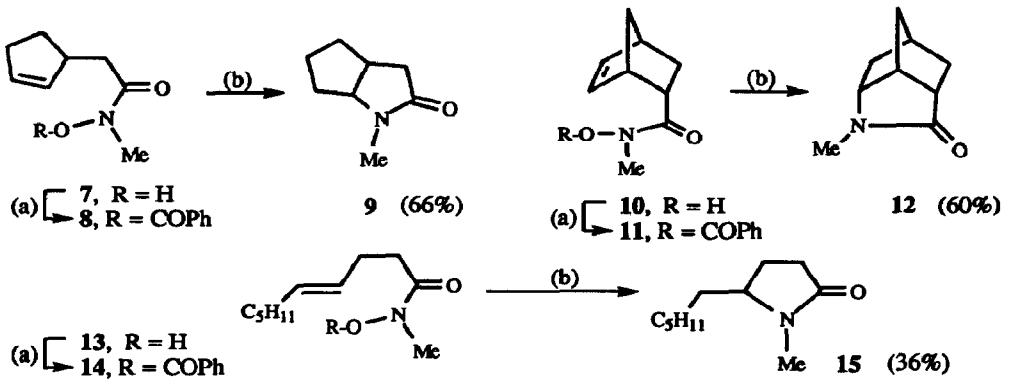


Scheme 1

Our approach to amidyl and carbamyl radicals relies on the easy cleavage of esters of hydroxamic acid derivatives (4 in scheme 1). The cleavage of ordinary esters with tributylstannane (X=O in scheme 1), has

been described some time ago by Khoo and Lee,[4] but, as a method for radical deoxygenation, it is of very limited applicability. An efficient and synthetically useful solution to this problem had to await the discovery of the Barton-McCombie reaction, involving xanthates and other thiocarbonyl derivatives (X=S; R"=SMe; OPh; imidazolyl, etc..).[5] The much higher affinity towards stannyl radicals of a thiocarbonyl group as compared with that of a carbonyl group shifts the equilibrium in equation 1 much further to the right in the former case than in the latter. The result of a greater concentration of the intermediate radical **2** is a larger fragmentation rate and hence a longer and more efficient chain length. Replacing an oxygen atom by sulfur in this intermediate must also have a significant and probably favourable influence on the actual rate constant of the fragmentation step. It is known for instance that, in contrast to xanthates (R"= SMe), thiocarbamates (e.g. R"= NMe_2) are poor substrates in the Barton-McCombie reaction.[5a]

Deoxygenation of alcohols by the Khoo and Lee procedure is thus only practical in situations where the final carbon radical is particularly stabilised (e.g. by resonance), since the fragmentation step is then sufficiently fast. In the same way as for esters of oximes, it may be argued that the weakness of the N-O bond in the corresponding hydroxamic acid derivatives **4** should also strongly favour the fragmentation of the radical adduct **5**. This would compensate for a not very effective initial addition of stannyl radicals onto the carbonyl group (equation 2), and provide thus a useful access to amidyl and other related radicals, in view of the accessibility of hydroxamic acid derivatives.

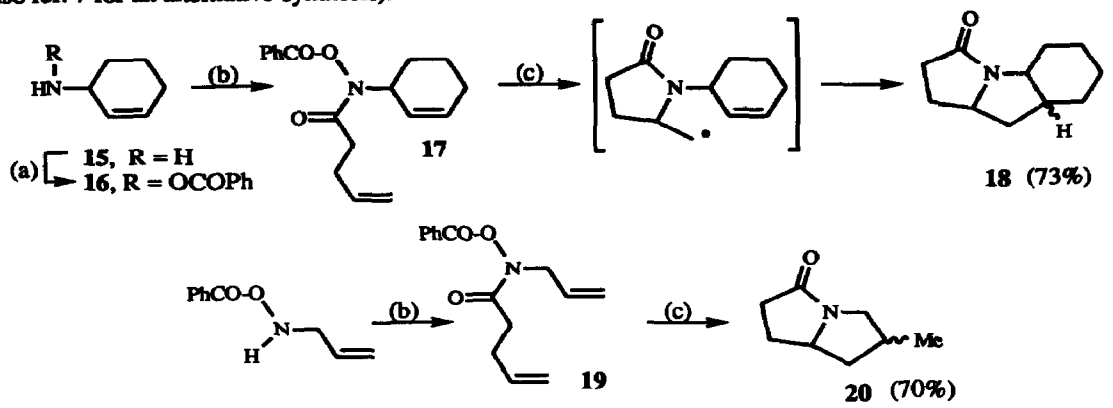


(a) PhCOCl / Pyridine; (b) Bu_3SnH (cat. AIBN, addition over 4 hours) / cyclohexane.

In the event, slow addition of tributylstannane and AIBN to a refluxing solution of benzoate **8** (made from 2-cyclopentenylacetyl chloride via hydroxamic acid **7**) in degassed cyclohexane produced smoothly bicyclic lactam **9** in 66% yield through capture of the intermediate iminyl radical by the internal olefin. The same reaction was readily applied to benzoates **11** and **14** which afforded the expected lactams **12** and **15** in 70% and 36% yield respectively.

The amidyl radicals could be easily incorporated in a number of cascade reactions (scheme 2). For example, benzoate **17**, derived from 2-cyclohexenylamine by oxidation with dibenzoyl peroxide[6] and acylation of the intermediate O-benzoyl hydroxylamine **16** with 4-pentenoyl chloride, gave tricyclic lactam **18** in 73% yield as an essentially 1:1 mixture of diastereoisomers when it was exposed to tributylstannane under similar conditions.[7] In the same way, compound **19**, prepared by a similar route from allylamine, afforded lactam **20** as a 2:1 mixture of epimers in comparable yield (70%). This compound had been

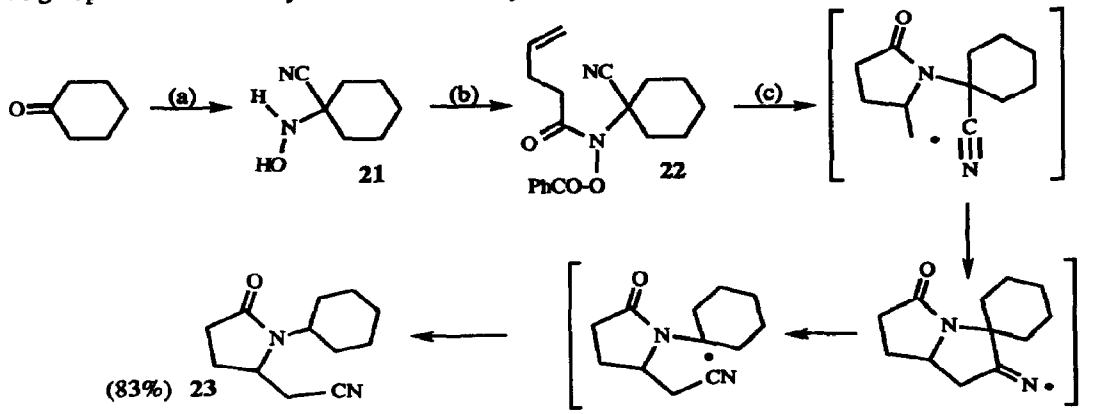
prepared by Esker and Newcomb[3a] using an identical sequence but a different amidyl radical precursor (see also ref. 7 for an alternative synthesis).



(a) Dibenzoyl peroxide / THF; (b) 4-Pentenoyl chloride / pyridine;
(c) Bu_3SnH (cat. AIBN, addition over 4 hours) / cyclohexane.

Scheme 2

A more interesting sequence took place with benzoate 22. This precursor was swiftly assembled from cyclohexanone, through reaction with hydroxylamine hydrochloride and sodium cyanide to give hydroxylamine 21,[8] followed by acylation with 4-pentenoyl chloride and benzoylation. Slow addition of tributylstannane resulted in the formation of nitrile 23, isolated as a crystalline solid (m.p. 82°C, from ether) in 83% yield. As depicted in Scheme 3, the formation of this compound implies an efficient transfer of the nitrile group[9] after the initial cyclisation of the amidyl radical.

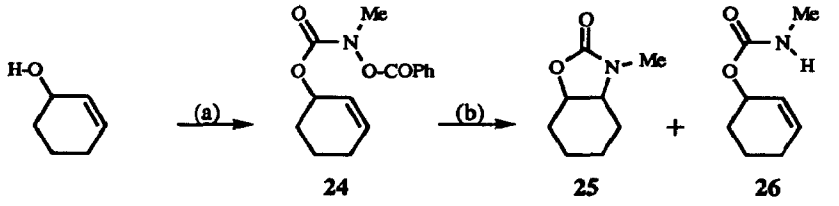


(a) $NH_2OH.HCl$ / NaCN / H_2O; (b) 4-pentenoyl chloride / Pyridine; PhCOCl / Pyridine
(c) Bu_3SnH (cat. AIBN, addition over 4 hours) / cyclohexane.

Scheme 3

This approach to amidyl radicals could be easily extended to the preparation of carbamyl radicals. These species have hardly been studied in the past, and little is known about their reactivity, especially concerning their propensity to undergo 5-exo cyclisations.[10] Starting from 2-cyclohexenol, we therefore

prepared the required benzoate **24** by treating the corresponding imidazolide wih N-methyl hydroxylamine followed by benzoylation. Slow addition of tributylstannane and a catalytic amount of AIBN to a refluxing solution of **24** in cyclohexane produced the desired cyclic carbamate **25**, along with uncyclised material **26** in a ratio of 40 / 60. The isolated yield of **25** was however only 20%. The cyclisation step is clearly slower than in the amidyl case but, nevertheless, its success opens the way to the synthesis of cyclic amino alcohols of controlled relative stereochemistry. Important compounds of this type include the aminocyclitols, conduramines, aminocyclopentitols (e.g. the mannostatins) etc.., some of which are potent glycosidase inhibitors.[11]



24 **25** **26**

(a) Carbonyl diimidazole; MeNHOH.HCl / Et_3N / THF; PhCOCl / Pyridine;
(b) Bu_3SnH (cat. AIBN, addition over 4 hours) / cyclohexane.

This route to amidyl and carbamyl radicals has the merits of simplicity, mildness, and efficiency. The same approach should be applicable to the generation of other nitrogen centered radicals by again taking advantage of the weakness of the N-O bond. Further studies along these lines are in progress.

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