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Iminyl Radicals by Stannane Mediated Cleavage of Oxime Esters

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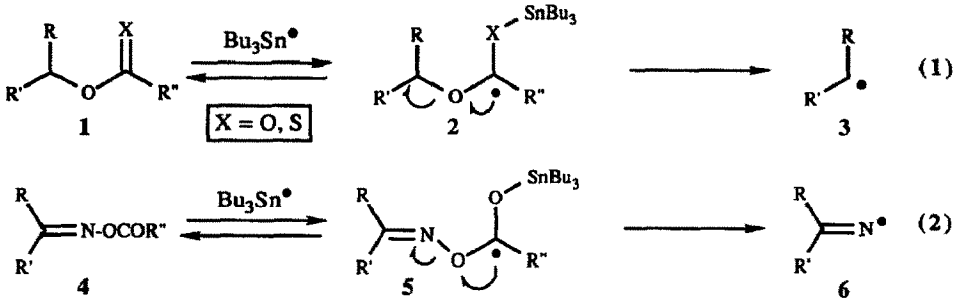
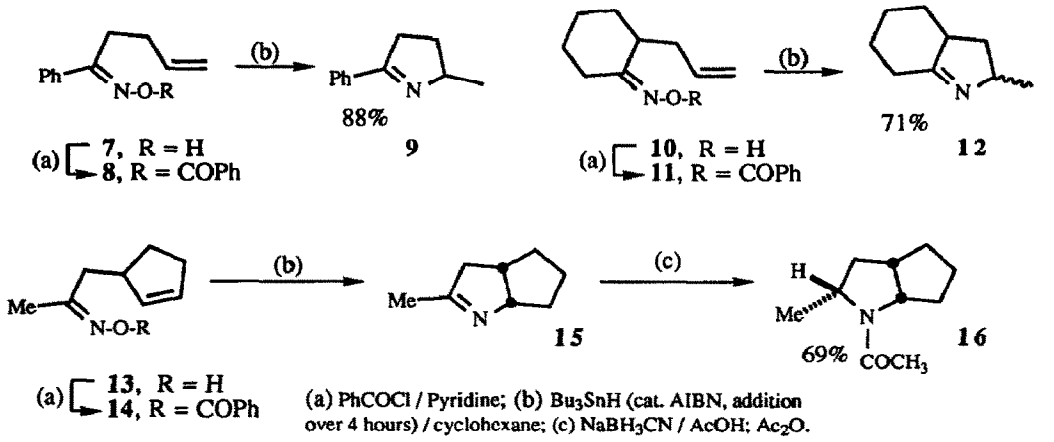
Abstract : Oxime benzoates react with tributylstannane in the presence of AIBN to give iminyl radicals which can be captured by an internal olefin.

Despite the explosive growth in the use of radical reactions which has swept organic synthesis in the past few years, nitrogen centred radicals and iminyls in particular have not yet attracted the attention they deserve[1,2]. This can be traced to a large extent to a lack of convenient and mild methods for generating such species. As part of a general study of the reactivity and synthetic potential of iminyls, we recently showed that the reaction of sulfenimines with tributystannane or the Barton decarboxylation of O-carboxymethyl oximes represented useful routes to these intermediates[3]. Another promising approach, still in its preliminary stages however, involved the reduction of oxime esters with nickel powder in acetic acid[3d]. In this Letter, we describe yet another method based on the cleavage of oxime benzoates with tin centered radicals.

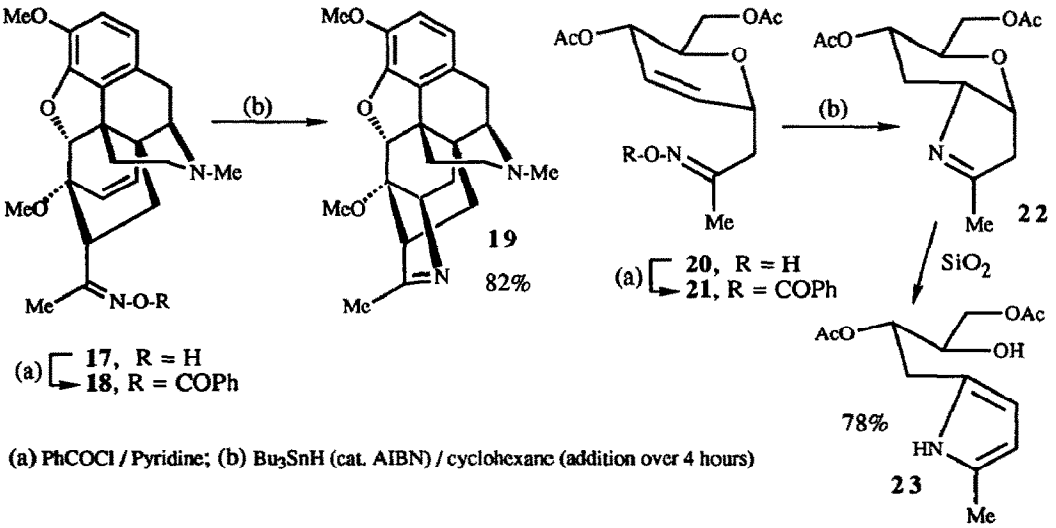


The reaction of ordinary esters with tributylstannane[4] has not found widespread use as a method for radical deoxygenation as compared with that based on xanthates and other thiocarbonyl derivatives[5] (the Barton-McCombie reaction). The reason lies in the much lower reactivity of a carbonyl towards tin radicals as compared with a thiocarbonyl group causing the equilibrium in equation 1 to shift much more to the left in the former case than in the latter. The consequence of a lower concentration of the intermediate adduct radical 2 is a slower fragmentation rate and hence a shorter chain length. The deoxygenation via carboxylic esters is thus only practical in cases where the final radical produced is especially stabilised (e.g. by resonance), the fragmentation step becoming as a result reasonably rapid.

In the case of esters of oximes, it may be argued that the weakness of the N-O bond should also strongly favour the fragmentation step and therefore would compensate for a not very effective initial addition of stannyl radicals onto the carbonyl group (equation 2). If successful, such a process would be particularly useful in view of the ease with which oxime esters can be prepared from almost any ketone or aldehyde.

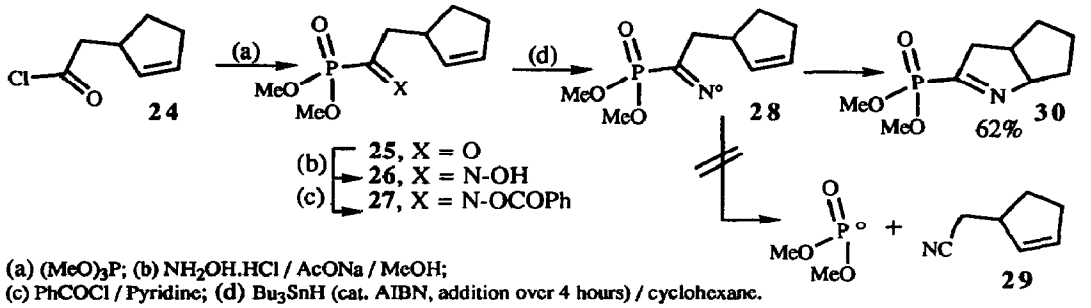


In the event, slow addition of tributylstannane and AIBN to a refluxing solution of oxime benzoate **8** in degassed cyclohexane produced pyrrolenine **9** in excellent yield (88%) through capture of the intermediate iminyl radical by the internal olefin. In line with earlier observations[4a], the corresponding acetate was less reactive towards the stannane so we only used oxime benzoates in our study as shown by the following examples.



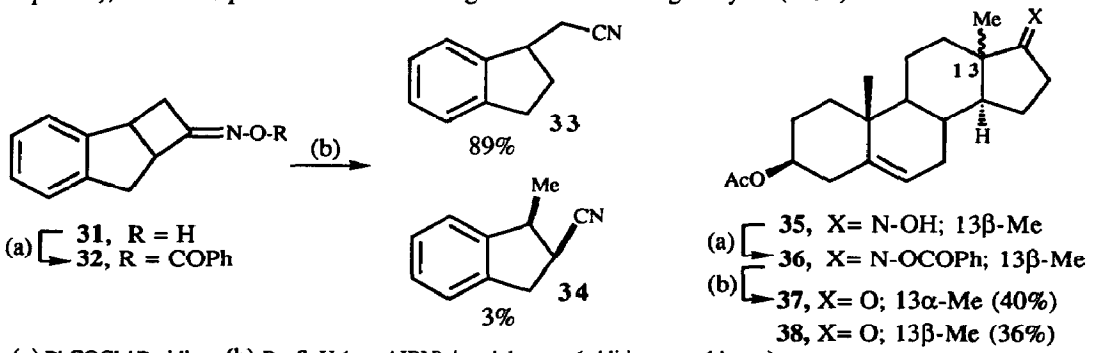
Thus benzoate **11** derived from 2-allylcyclohexanone gave the expected pyrrolenine **12** in 71% yield as a 60:40 mixture of diastereomers. In the same way, compound **14** afforded derivative **15** which was in

this case reduced *in situ* with sodium cyanoborohydride and acetylated to give finally amide **16** in 69% yield as one isomer since reduction takes place from the least hindered exo face. An efficient cyclisation of the much more complex substrate **18**, obtained through cycloaddition of methyl vinyl ketone with thebaine[6], could also be accomplished by the same procedure. The polycyclic product **19**, isolated in 82% yield, was accompanied by a small amount (8%) of oxime **17**. The sugar derivative **21**, easily made from tri-O-acetyl glucal[7], also cyclised smoothly; however, on attempted purification on silica, the primary product **22** underwent elimination and aromatisation to pyrrole **23** in 78% overall yield. This example shows that only the oxime benzoate is cleaved by the stannyl radicals; the other ester groups are not affected.



(a) $(MeO)_3P$; (b) $NH_2OH.HCl$ / AcONa / MeOH;
(c) PhCOCl / Pyridine; (d) Bu_3SnH (cat. AIBN, addition over 4 hours) / cyclohexane.

An interesting type of oxime which also turned out to be a good substrate for the cyclisation is exemplified by compound **27**, obtained by Arbusov reaction of acid chloride **24** with trimethyl phosphate[8], followed by oximation and benzoylation. We feared in this case that the intermediate iminyl radical would undergo ß-scission to nitrile **29** faster than the desired cyclisation. Fortunately, this did not turn out to be the case and pyrrolenine **30** was isolated in 62% yield along with a little (3%) oxime **26**. It is worthy of note that compounds such as **30** are immediate precursors to phosphonate analogues of some proline derivatives (e.g. Ramipril®[9]), which are potent inhibitors of Angiotensin Converting Enzyme (ACE).



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

β-Scission of strained iminyl radicals can nevertheless be a useful synthetic transformation as we[2c,d] and others[10] had shown earlier. For example, under the usual reaction conditions, benzoate **32** was converted into nitrile **33** in high yield (89%); a small quantity (3%) of isomeric nitrile **34** was also isolated,

arising from opening to the less stable intermediate primary carbon radical. The present method however appears to be less effective than our previous processes[3d] for accomplishing the epimerisation of the 13-position of steroids through opening and reclosure of the D-ring of iminyls derived from 17-ketosteroids. Thus upon reaction of benzoate **36** with tributylstannane, the corresponding 13-episteroid **37** was only obtained in 40% yield. The natural isomer **38** was the other major product (36%). A small amount (6%) of of a mixture of both 3ß-hydroxyketones was also isolated. It is clear that the oxime benzoate is less reactive than the sulfenimide causing a build-up in stannane concentration so that the imine radical is reduced before undergoing the D-ring opening-ring closure sequence.

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