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Iminyl Radical Generation via Iminodithiocarbonate Group Transfer

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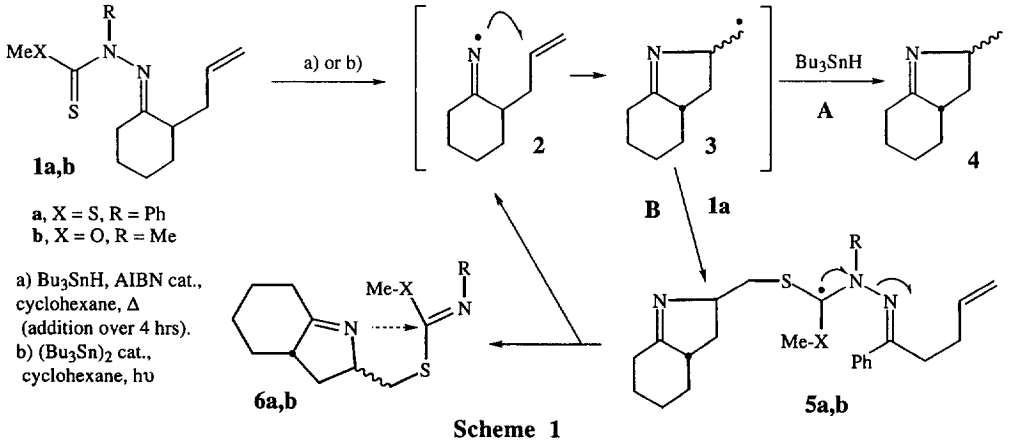
Abstract : Irradiation with a sun lamp of thiocarbazone derivatives related to **1a** in the presence of small amounts of hexabutylditin provides adducts arising from the reaction of an iminyl radical followed by transfer of an iminodithiocarbonate group. © 1997 Elsevier Science Ltd.

As part of our work on the chemistry of iminyls, amidyls and related nitrogen centered radicals,[1] we found that thiocarbazone derivatives were versatile and convenient precursors for such species.[1g] For example, thiocarbazone **1a** undergoes a homolytic fragmentation of the relatively weak N-N bond upon addition of stannyl radicals under conditions a) to give the corresponding iminyl **2** which readily undergoes 5-exo-cyclisation. Finally, hydrogen abstraction from tributyltin hydride (path A) provides pyrrolenine **4** in good yield. This method could be moreover adapted to allow measurement of the rate constant for such cyclisations which were found to be about one order of magnitude slower than those of the corresponding saturated carbon radical.[2] The thiocarbazone progenitors are simply made by condensation of a hydrazide **7** of general formula H_2N-NRC=S(XMe) with a ketone or aldehyde. Such hydrazides are readily accessible and easily stored (we have used **7a**: R=Ph, X=S; **7b**: R=Me, X=S; and **7c**: R=Me, X=O).[3]



Scheme 1

Our initial aim, when we contemplated the possibility of employing thiocarbazones as precursors for nitrogen centered radicals, was in fact to avoid the use of stoichiometric tin hydride: we hoped that the

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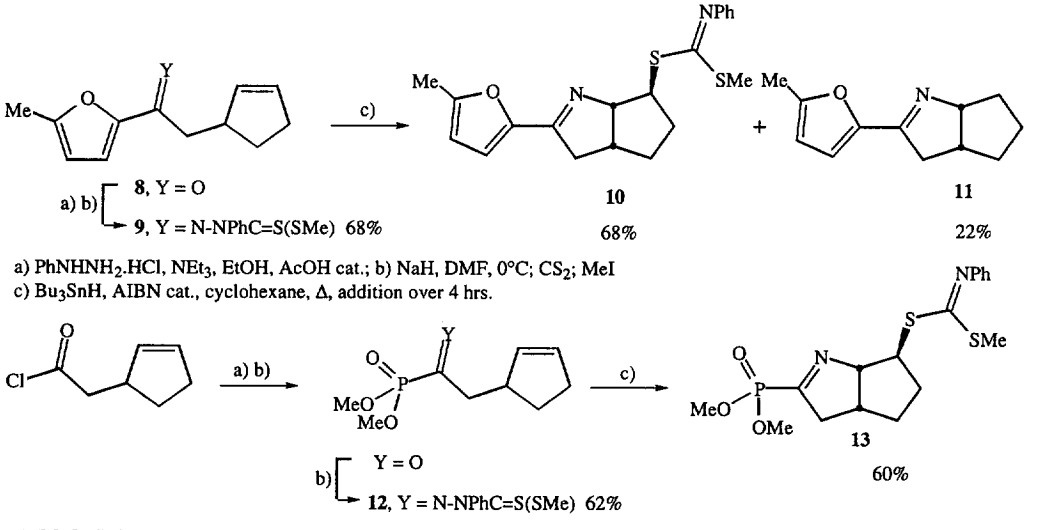
thiocarbonyl group would be sufficiently reactive to capture the carbon radical **3** arising from the cyclisation step and thus sustain the chain reaction leading to **6a** (path B). An extra, sulfur containing functionality would hence be introduced and many of the problems associated with stannanes (premature reduction of intermediate radicals; purification; etc.), would in principle be circumvented. Unfortunately, our preliminary studies in this respect were disappointing, since the yield of **6a** did not exceed a modest 35% when a solution of **1a** in cyclohexane (conditions (b)) was irradiated with a sun lamp in the presence of 10% hexabutylditin.

The poor yield and the need to have hexabutylditin for some propagation to occur indicated that our difficulties were perhaps due to the formation of sulfur containing side products that were acting as inhibitors.[4] One obvious culprit is methanethiol, produced by an intramolecular ionic addition of the imine nitrogen to the iminodithiocarbonate group in **6a**, as shown by the dotted arrow in Scheme 1. If this were the case, the product would be indirectly (and ironically) inhibiting its own formation. Curiously, however, replacing the sulfide sulfur in the precursor with oxygen, as in **1b**, did not result in any transfer leading to the corresponding adduct **6b** (Scheme 1) even though such precursors react normally with tributyltin hydride to give the usual cyclised derivatives (e. g. **4**). The reason for this behaviour is not clear but it is possible that in this instance, it is the fragmentation of the intermediate adduct **5b** in the desired direction that becomes too slow. Nevertheless, strong support for the hypothesis that inhibition, at least in the series where X = S, is due to an ionic interaction between the iminyl nitrogen and the iminodithiocarbonate group came from a later, serendipitous, observation which allowed us at the same time to improve the process considerably in several systems.



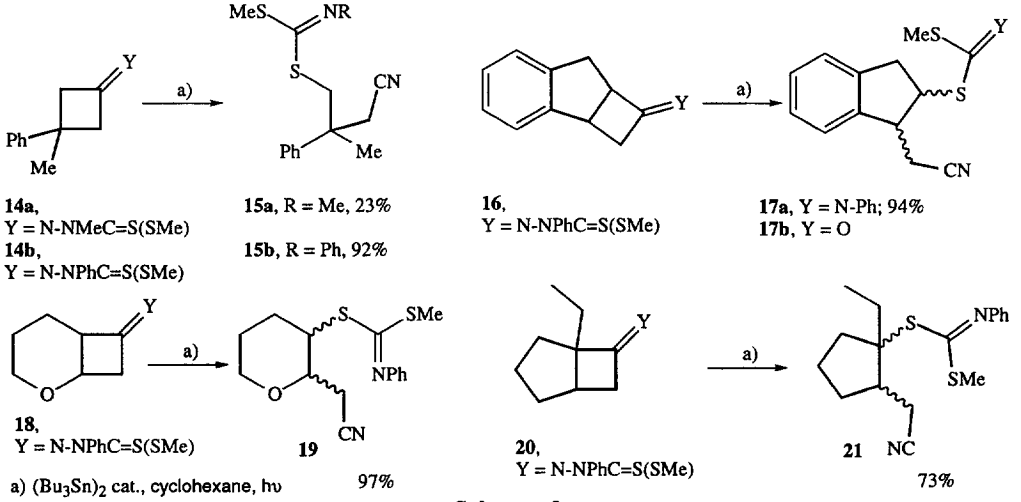
Scheme 2

When tributyltin hydride and a small amount of AIBN were added slowly to a refluxing solution of thiocarbazone **9** in cyclohexane, the reaction afforded mostly the iminodithiocarbonate **10** (68%) instead of the expected product of reductive cyclisation **11**, which was formed in only 22% yield (Scheme 2). Electronically, the situation is very similar to the previous example but the geometry of the molecule is now quite different: the cis junction of the two five-membered rings and the exo disposition of the

iminodithiocarbonate side chain makes any nucleophilic attack by the ring nitrogen very unlikely. In this case therefore, the transfer of the sulfur containing group becomes unusually efficient, explaining why, even with a stoichiometric amount of tin hydride, the functionalized product **10** dominates. Thiocarbazone **9** was prepared as shown from ketone **8**, itself made by reaction of 2-methylfuran with 2-cyclopentene-1-acetic acid and trifluoroacetic anhydride.[5] In this instance, direct condensation with hydrazide **7a** was sluggish and low-yielding.

The need to move away the imine nitrogen from the iminodithiocarbonate group was further corroborated by an experiment involving another thiocarbazone where the pyrrolenine has a similar fixed geometry. Thus, irradiation with visible light of a degassed solution of **12**, obtained by an Arbuzov reaction of 2-cyclopenteneacetyl chloride with trimethyl phosphite[1d] followed by condensation with hydrazide **7a**, in benzene in the presence of 15% of hexabutylditin resulted in the formation of 60% of pyrroline **13** accompanied by 28% of starting material.

Another solution in accord with the above reasoning consists in reducing considerably the nucleophilicity of the nitrogen by converting the iminyl radical into a nitrile. This may be accomplished by exploiting the rapid opening of cyclobutyliminyl radicals.[1b,6] In this way, interference of the nitrogen is no longer possible and an efficient propagation of the chain reaction would be expected. The examples in scheme 3 below illustrate this variation.



14a, Y = N-NMeC=S(SMe)
14b, Y = N-NPhC=S(SMe)
15a, R = Me, 23%
15b, R = Ph, 92%
16, Y = N-NPhC=S(SMe)
17a, Y = N-Ph; 94%
17b, Y = O
18, Y = N-NPhC=S(SMe)
19 97%
20, Y = N-NPhC=S(SMe)
21 NC 73%
a) $(Bu_3Sn)_2$ cat., cyclohexane, hυ

Scheme 3

The thiocarbazone precursors were easily obtained by direct condensation of hydrazides **7** with the requisite cyclobutanones. The cyclobutanones were prepared either by cycloaddition of dichloroketene to the appropriate olefin[7a,b] followed by dechlorination with zinc powder in acetic acid or, in the case of **20** (Y=O), by an intramolecular cycloaddition of the ketene derived from 2-ethylidene-6-heptenoyl chloride followed by catalytic reduction.[7c,d]

A preliminary experiment indicated that the N-phenyl derivatives were much superior to the corresponding N-methyl analogues. Thus, irradiation with visible light of a solution of **14a** in cyclohexane in the presence of 5 mol% hexabutylditin resulted in the formation of only 23% of nitrile **15a** and 57% of the

starting material was recovered. In contrast, **14b** was converted under the same conditions into **15b** in 90% yield. It appears therefore that substituents both on the nitrogen and on the thiocarbonyl carbon (cf. **1b** where X=O and which does not transfer) have a strong influence on the rate of fragmentation of the intermediates corresponding to **5**.

As a consequence of this observation, N-Ph derivatives were used for the remaining examples. Thus compound **16** derived from 2,2a,7,7a-tetrahydrocyclobuta[a]inden-1-one,[7a] afforded nitrile **17a** (94%) as a 12:88 mixture of *cis* and *trans* isomers respectively . These proportions were determined after hydrolysis with hydrochloric acid of the phenyliminyl moiety leading to dithiocarbonate **17b**. The ring opening reaction to give the more stable secondary radical was also efficient starting with compound **18**, accessible from 2-oxa-bicyclo[4.2.0]octan-7-one.[7b] Nitrile **19** was produced almost quantitatively (97%) as a (35:65) mixture of *cis* and *trans* isomers. Finally, the reaction was extended to a case where opening of the cyclobutyliminyl leads to a tertiary carbon radical. We were concerned initially that such a radical might be too stabilised to propagate the chain. In the event, the reaction of **20** turned out to be somewhat slower than usual (irradiation for 24 hours) and required addition of three 5 mol% portions of hexabutylditin but provided nevertheless a good yield (73%) of the corresponding iminothiocarbonate **21**.

Several attempts to replace hexabutylditin and light by initiation with peroxides were unfortunately not successful. Irradiation of a solution of **14b** in cyclohexane with a focused xenon arc (Xenophot) in the absence of hexabutylditin resulted in the formation of only 30% of **15b** together with 60% of recovered starting material. Clearly, the chain process in this new transformation is easily inhibited. The cleavage of the N-N bond is apparently be relatively slow and the optimum substituents on the thiocarbazone moiety still have to determined. Nevertheless, this original method for generating and capturing iminyl radicals allies mildness and simplicity, and allows the expedient elaboration of highly functionalised structures that would otherwise be accessible only with difficulty. The presence of a sulfur group in the end product represents a powerful synthetic asset.

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3. For example, hydrazide **7b** is made in one step from methylhydrazine, carbon disulfide, and methyl iodide whereas **7a** requires the reaction of benzaldehyde phenylhydrazone with carbon disulfide and methyl iodide followed by heating with an equimolar amount of phenylhydrazine in ethanol / hydrochloric acid; see: Jensen, K. A.; Anthoni, U.; Holm, A. *Acta Chem. Scand.* **1969**, *23*, 1916-1934.
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