

Synthesis of non-aromatic heterocyclic compounds through free-radical reactions

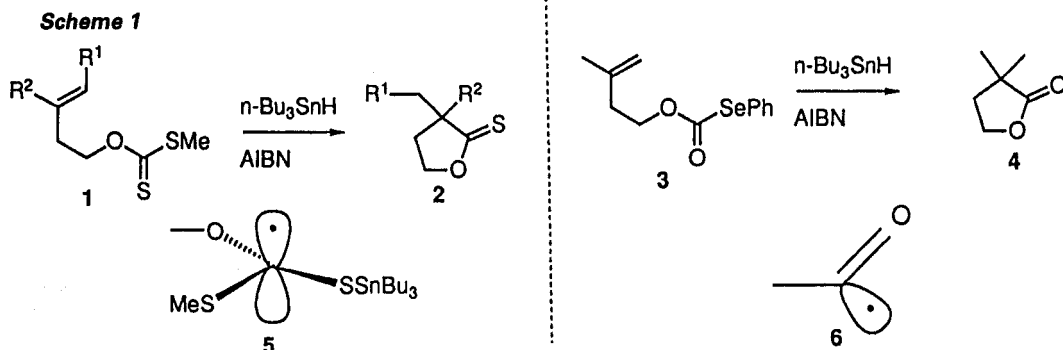
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Abstract – Various non-aromatic heterocyclic compounds, including lactones, lactams, thiolactams, chromanones, and pyrrolines are obtained by reactions involving the intramolecular addition of carbon-centered ene radicals to carbon-carbon multiple bonds.

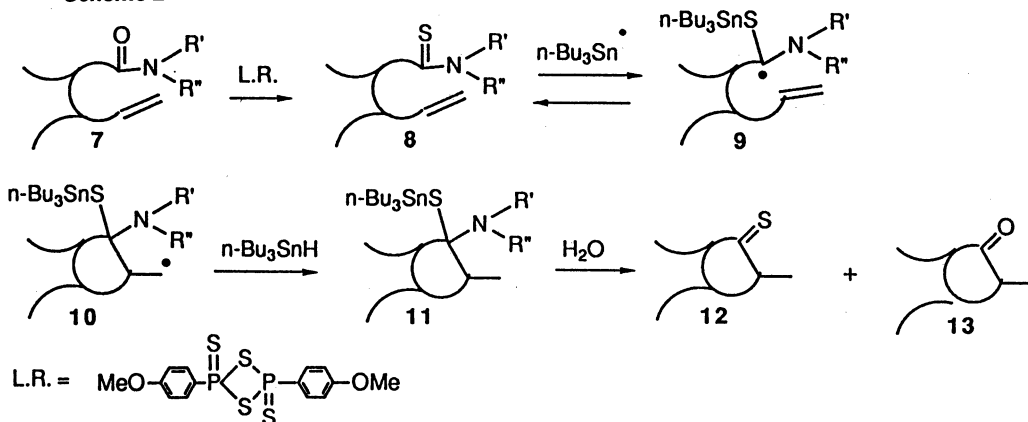
A few years ago we reported on an efficient synthesis of α -alkylidene γ -lactones by the $n\text{-Bu}_3\text{SnH/AIBN}$ induced cyclization of phenylselenocarbonate derivatives of homopropargylic alcohols and on the cyclization of O-(4-phenylbut-3-yn-1-yl)-S-methyl dithiocarbonate.¹ Synthetic methods based on these two reactions were further studied and extended in our and in other laboratories. While the $n\text{-Bu}_3\text{SnH/AIBN}$ induced cyclization of selenol esters of unsaturated carbonic and carboxylic acids proved to be a powerful and versatile tool for the synthesis of cyclic ketones and lactones,^{2–6} the analogous reaction of thiono derivatives of unsaturated carbonic and carboxylic acids has found only limited synthetic applications.^{7–11}

We have found that the $n\text{-Bu}_3\text{SnH/AIBN}$ induced cyclization of O-alkenyl-dithiocarbonate bearing a double bond activated by a phenyl group **1** ($R^1 = \text{Ph}$, $R^2 = \text{H}$) results in the formation of the corresponding thionolactone **2** in 77% yield but when an unactivated double bond is involved as in **1** ($R^1 = R^2 = \text{H}$) the yield drops down to 51%, and when the double bond is sterically hindered as in **1** ($R^1 = \text{H}$, $R^2 = \text{Me}$) cyclization is retarded and only traces of the corresponding thionolactone **2** were detected (Scheme 1).⁸ In contrast, the cyclization of the analogous O-alkenyl-phenylselenocarbonate **3** afforded the corresponding dimethyl- γ -lactone **4** in quantitative yield.² The rates of cyclization of dithiocarbonates are clearly much more dependant on the reactivity of the double bond and on the steric accessibility to it than are those of the corresponding selenoesters. This difference derives from the different nature of the radicals participating in the ring closure. The $n\text{-Bu}_3\text{Sn}^*$ induced homolysis of the C—Se bond in the selenocarbonate results in alkoxy-carbonyl radicals of type **6**. This is a reactive σ radical which undergoes a fast intramolecular addition to the double bond even when the double bond is unactivated and sterically hindered. In the reaction with dithiocarbonates, tributylstannyl radicals add to the thiono sulfur group to give a trihetero-substituted radicals of type **5** which have a strong p -character. These radicals have higher steric requirements and are effectively stabilized by the heteroatom substituents. As a consequence, cyclization rates are lower and more sensitive to supporting and impeding factors than those of analogous σ radicals **6**.



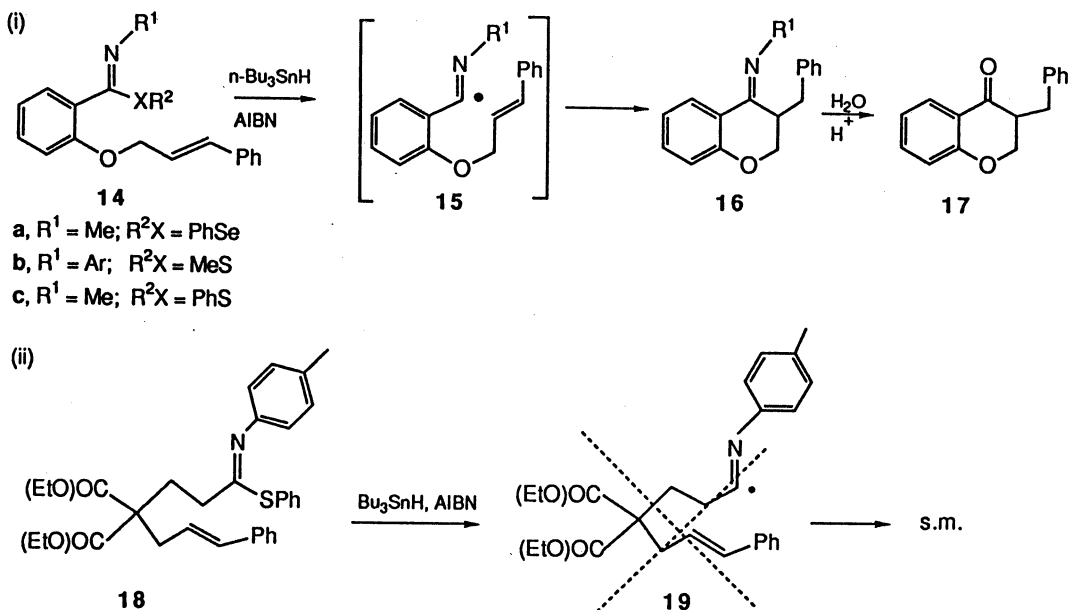
We examined also the potential of thioamides as substrates for free radical cyclizations mediated by $n\text{-Bu}_3\text{SnH}$.⁹ Relatively non-reactive secondary amides **7** may be used for the preparation of thioamides. It was considered that thioamides **8** may function as free radical precursors, to be generated by $n\text{-Bu}_3\text{SnH}$ at a predetermined stage of a multi-step synthesis as shown in Scheme 2. Such a reaction would give a cyclic thiocarbonyl or carbonyl product **12** or **13**. It was however found that due to the strong stabilizing effect exerted by the nitrogen atom on the adduct radical **9**, it is not sufficiently reactive to maintain an efficient chain reaction through ring closure into radical **10**. Processes of the type described in Scheme 2 may be synthetically useful only when the stabilizing power of the nitrogen atom in **9** is reduced by an electron withdrawing substituent R' .

Scheme 2



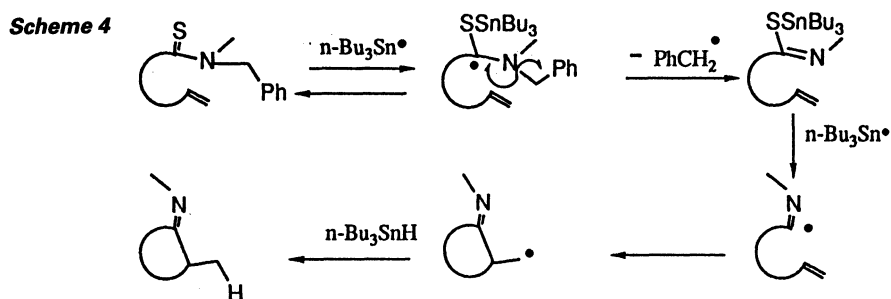
An alternative attractive avenue for the use of thioamides as substrates in free radical cyclization designated for the preparation of cyclic carbonyl compounds involves their conversion into carbon centered imidoyl radicals.^{9,12} We have found (Scheme 3, i) that phenylselenoimidate **14a** is converted in very good yield into the chromanone **17** by a process which involves the generation of the imidoyl radical **15** through stannyl radical mediated homolysis of a C—Se bond. Methylthioimidates, for example **14(R²X = MeS)** which are readily obtained from the corresponding thioamides, were tested as possible substitutes for the more toxic selenoimidates. We found that methylthioimidate **14b** does not react with $n\text{-Bu}_3\text{SnH/AIBN}$, but phenylthioimidate **14c** undergoes cyclization on treatment with $n\text{-Bu}_3\text{SnH/AIBN}$, giving after hydrolysis, the chromanone **17** in good yield. Namely, the labilization of the carbon-sulfur bond by the phenyl group in **14c** as compared with the methyl group in **14b** is sufficient to allow the homolysis of the C—S bond by the attacking tin radical in thioimidates derived from an aromatic carboxylic acid. Unfortunately the labilizing power of the phenyl group on the

Scheme 3

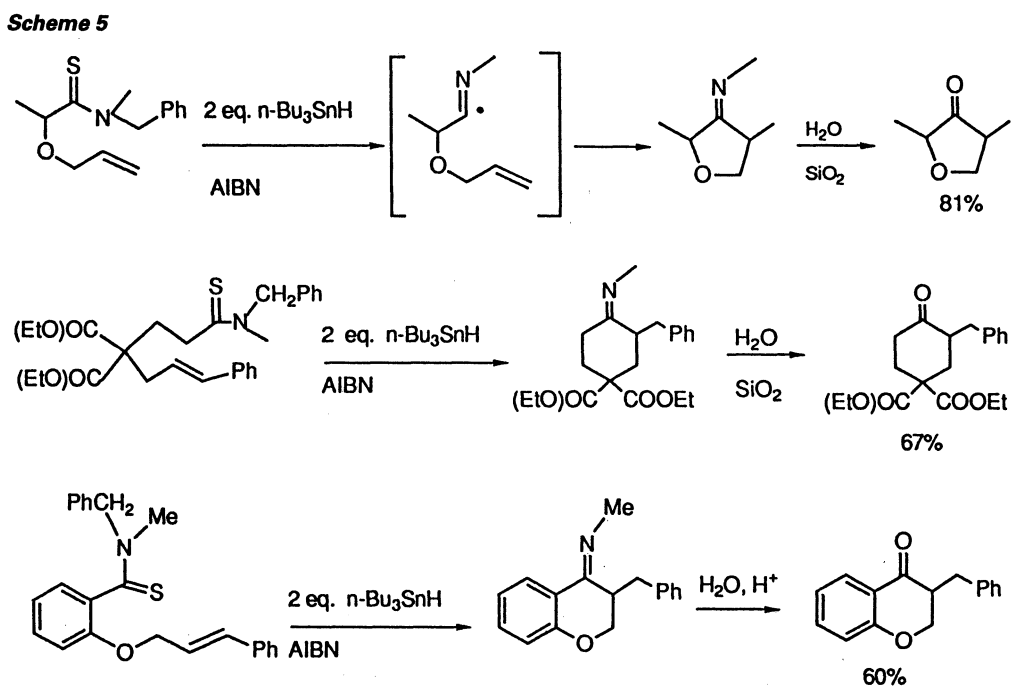


stronger C—S bond of thioimide derivatives of an aliphatic carboxylic acid is not sufficient and the phenylthioimide **18** was recovered unchanged after treatment with $n\text{-Bu}_3\text{SnH/AIBN}$ under standard conditions. Clearly a stronger activating effect should be applied to the C—S bond of the thioimides derived from aliphatic acid.⁹

A tin substituent on a divalent sulfur atom labilize the adjacent C—S bond.^{12,13} We therefore examined the possibility of using tributyltin thioimides instead of alkylthio or phenylthio-imidates. Tributyltin thioimides can be readily prepared from thioamides either by treatment with a base, like NaH and $n\text{-Bu}_3\text{SnCl}$ or by reaction with tributyltin oxide. Treatment of crude tri- n -butyltinthio imidates with $n\text{-Bu}_3\text{SnH/AIBN}$ resulted in the formation of carbon-centered imidoyl radicals and their intramolecular addition to suitably positioned double bond affording cyclic ketone imines in good yield. However, in order to avoid the handling of sensitive tri- n -butyltinthioimides we conceived an alternative method for the generation of imidoyl radicals which is based on a double elimination process of N -benzyl N -(methyl)thioamides (Scheme 4).⁹ The tri- n -butyltin radical adds to the thiocarbonyl in a reversible manner, the resulting radical is not sufficiently reactive to undergo addition to the double bond under standard conditions. However we envisaged that an irreversible β -cleavage of the stabilized benzyl radical will occur, and the desired tri- n -butyltinthioimide will be formed. The butyltinthioimide will in turn react with a second equivalent of tin radical to give the desired carbon-centered N -alkenylimidoyl radical through cleavage of the destabilized C—S. This reactive ene radical is isoelectronic to carbonyl and to vinyl radicals, and is expected to undergo rapid addition to a suitably positioned C-C double bond.



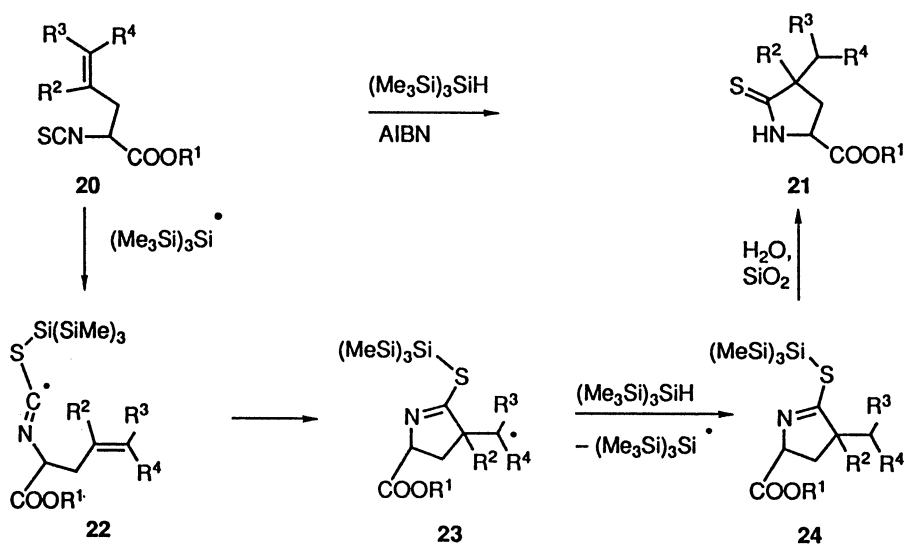
The three examples given in Scheme 5 show that the method is suitable for the cyclization of both aliphatic and aromatic thioamides, for the preparation of both 5- and 6-membered ring ketones.⁹



This series of experiments leads to the conclusion that, in cyclization involving addition to double bonds, σ carbon-centered ene-radicals are better intermediates than their synthetically equivalent *p*-alkyl radicals. While "simple" secondary thioamides are not suitable for *n*-Bu₃SnH / AIBN induced cyclization, *N*-benzyl(*N*-methyl)thioamides which may function as precursors to carbon-centered imidoyl radicals are excellent substrates for this reaction.

We have recently reported on a new method for the synthesis of γ - and δ -thiolactams, based on the intramolecular addition of carbon-centered tri-*n*-butyltinthioimidoyl radicals, to carbon-carbon double bonds.¹⁴ The tri-*n*-butyltinthioimidoyl radicals are generated in the reaction of *n*-Bu₃SnH / AIBN and isothiocyanates. Tri-*n*-butyltin hydride is an excellent reagent in free-radical chain reactions involving the generation of carbon-centered radicals from alkyl halides, sulfides and selenides.¹⁵ However the toxicity of tin compounds and reports on difficulties in removing traces of tin residues from reaction products have led several investigators to study the suitability of other hydrides for these purposes. Tris(trimethyl)silane (Me₃Si)₃SiH was found to be a good substitute to tri-*n*-butyltin hydride in many free radical reactions.¹⁶ We tested this reagent for the cyclization of isothiocyanates. Thus, treatment of isothiocyanates derivatives of glycine **20a-d** (0.02M solution in boiling toluene) with (Me₃Si)₃SiH (1.1equiv) and AIBN(0.15 equiv) afforded the corresponding pyrroglutamates **21a-d** in very good yield as shown in Scheme 6. Hydrolysis of **24** to **21** occurs spontaneously during chromatography. This is a general reaction which does not require the activation of the double bond (*cf.* **20a**). Furthermore it maintains its high regioselectivity yielding exclusively the 5-*exo* product even when the double bond is substituted at the site of attack of the imidoyl radicals as in the case of compound **20c**. These reactions are comparable to those mediated by tri-*n*-butyltin hydride. Only in the case of compound **20e**, in which the double bond is substituted by a phenyl group, cyclization does not occur under the standard conditions and starting material was recovered. However when this reaction was performed at higher concentration, namely 0.5M instead of 0.02M, the cyclic product **21e** was obtained in 57% yield. Also, when the reaction was performed under standard conditions but with diphenyldisulphide as catalyst (in addition to the usual AIBN) the thiopyrroglutamate **21e** was obtained in 40% yield.

Scheme 6



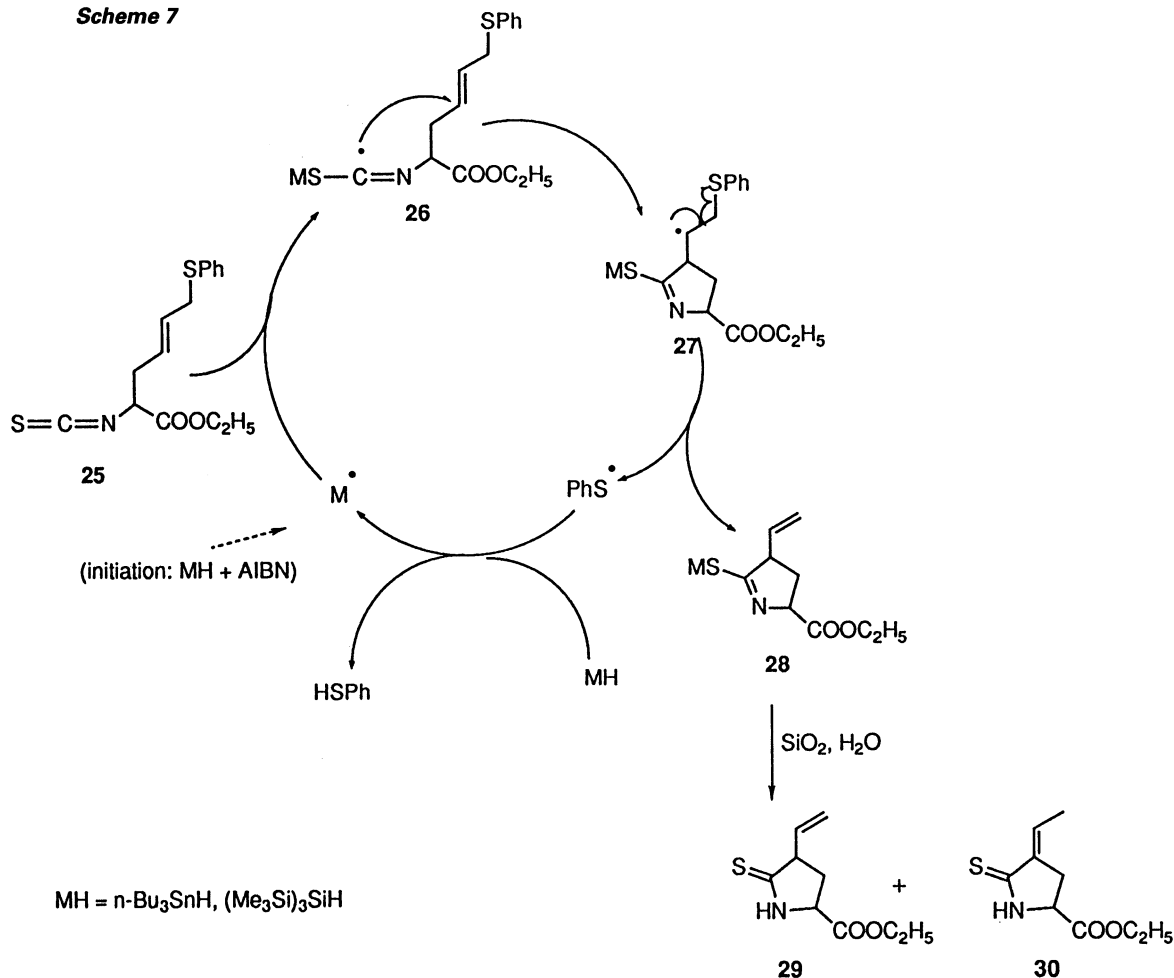
	initial c of 20	yield of 21
a, R ¹ = CMe ₃ ; R ² = R ³ = R ⁴ = H	[0.02M]	96%
b, R ¹ = CMe ₃ ; R ² = H; R ³ = R ⁴ = Me		93%
c, R ¹ = CMe ₃ ; R ² = Me; R ³ = R ⁴ = H		66%
d, R ¹ = Et; R ² = R ⁴ = H; R ³ = PhS		80%
e, R ¹ = Et; R ² = R ⁴ = H; R ³ = Ph	[0.5M]	0%
e, R ¹ = Et; R ² = R ⁴ = H; R ³ = Ph	[0.5M]	57%
e, R ¹ = Et; R ² = R ⁴ = H; R ³ = Ph	[0.02M], with PhS-SPh	40%

The rate of hydrogen atom transfer from $(\text{Me}_3\text{Si})_3\text{SiH}$ to alkyl radicals is about ten times lower than that of tri-*n*-butyltin hydride.¹⁶ It is possible that for reaction performed at a concentration of 0.02M hydrogen atom transfer from the $(\text{Me}_3\text{Si})_3\text{SiH}$ to the benzylic radical **23e** is too slow to maintain a viable chain reaction. Apparently at a concentration of 0.5M the rate of hydrogen atom transfer from $(\text{Me}_3\text{Si})_3\text{SiH}$ to **23e** becomes sufficiently high to support the chain reaction $20 \rightarrow 22 \rightarrow 23 \rightarrow 24$.

Catalysis by PhS-SPh probably involves generation of PhS^\bullet (with AIBN) which abstracts an H-atom from the silane and transfers it to the benzylic radical **23e**, etc. The tertiary dodecyl mercaptane used by Roberts¹⁷ for catalyzing various reductions with trialkylsilanes did not work in this case.

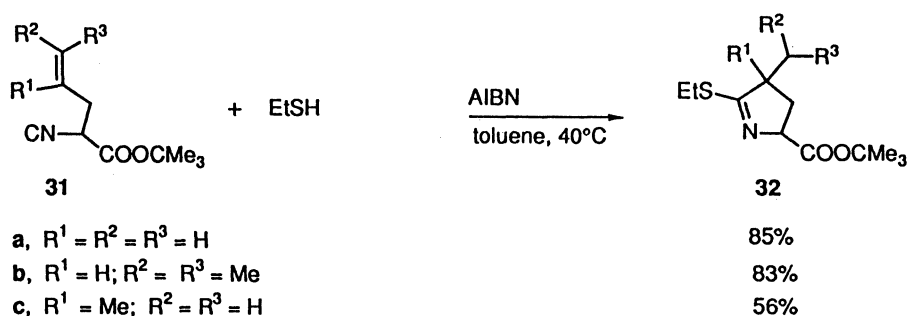
The intramolecular addition of carbon-centered N-alkenyl imidoyl radical like **22** to a double bond is thus an efficient process. It occurred to us that a potentially broader field of application would be opened up if instead of an isolated double bond more highly functionalized radical traps are used. It was visualized that isothiocyanate **25** may undergo the series of sequential reactions shown in Scheme 7 when treated with either $n\text{-Bu}_3\text{SnH/AIBN}$ or $(\text{Me}_3\text{Si})_3\text{SiH/AIBN}$. In the first step of the chain reaction the intermolecular addition of organostannyl or organosilyl radical M^\bullet to isothiocyanate **25** gives the imidoyl radical **26**, which affords a vinylpyrroline **28** through intramolecular addition and concerted or stepwise elimination of PhS^\bullet (through **27**). The eliminated phenylthiyl radical abstracts a hydrogen atom from the stannane or silane thus continuing the chain reaction. The stannylthio- or a silylthio- derivative **28** undergoes hydrolysis during chromatography over silica gel to give the pyroglutamic ester **29** and/or its thermodynamically more stable isomer **30**. It was found that reaction of isothiocyanate **25** with either $(\text{Me}_3\text{Si})_3\text{SiH}$ or $n\text{-Bu}_3\text{SnH}$ affords, under standard conditions a mixture of thiopyroglutamates **29** and **30** in 81% and 84% yield. Immediately after chromatography the **29** to **30** ratio was 1:2. But when kept in chloroform solution for 24 h at room temperature complete isomerization to the ethylden derivative **30** occurred.

Scheme 7

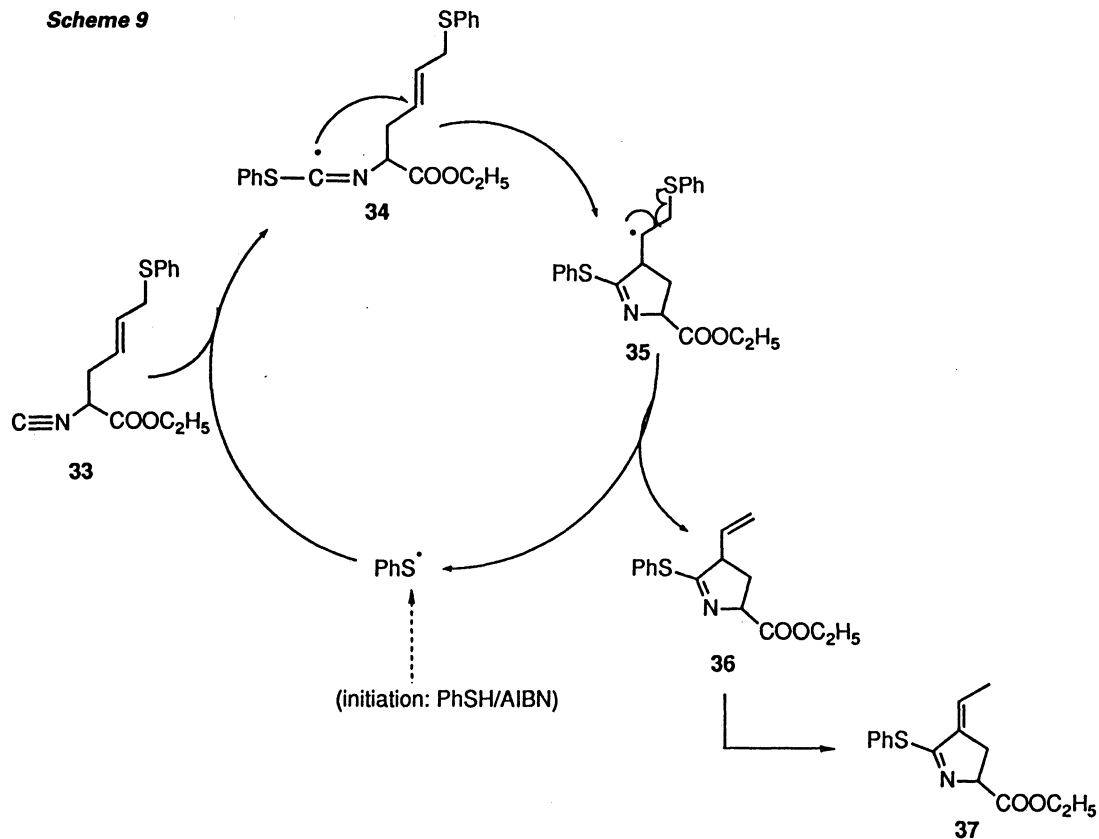


Free radical cyclization of alkenylisonitriles can be mediated by thiols.¹⁸ For example, isonitriles **31** derived from unsaturated α -amino acids react with ethanethiol/AIBN at 40°C giving the corresponding 2-alkylthiopyrroline in good yields (Scheme 8). This indicates that when a suitably positioned double bond is present in the molecule, the 5-exo ring closure predominates over the other theoretically possible cyclization transformations. On the grounds of the results described in Schemes 7 and 8 we conceived possible cyclization through formal isomerization of isonitrile **33** based on the sequential radical process described in Scheme 9. Accordingly, only a catalytic amount of thiol is required for generation of PhS^\bullet at the initiation stage. The propagation stage consists of a sequence of reactions involving intermolecular addition of PhS^\bullet to isonitrile **33** and intramolecular addition of the resulting phenylthioimidoyl radical **34** with concerted or stepwise elimination of PhS^\bullet (through **35**). Thus on treatment of isonitrile **33** with AIBN (0.15 equiv) and PhSH (0.15 equiv) in toluene at 110°C the 2-phenylthio-3-ethylidenepyrrroline **37** was obtained in good yield (70–85%). This compound evidently derives from spontaneous double bond migration in the cyclization product **36**. The reaction is independent of initial starting material concentration within the range of 0.2M–0.005M.

Scheme 8



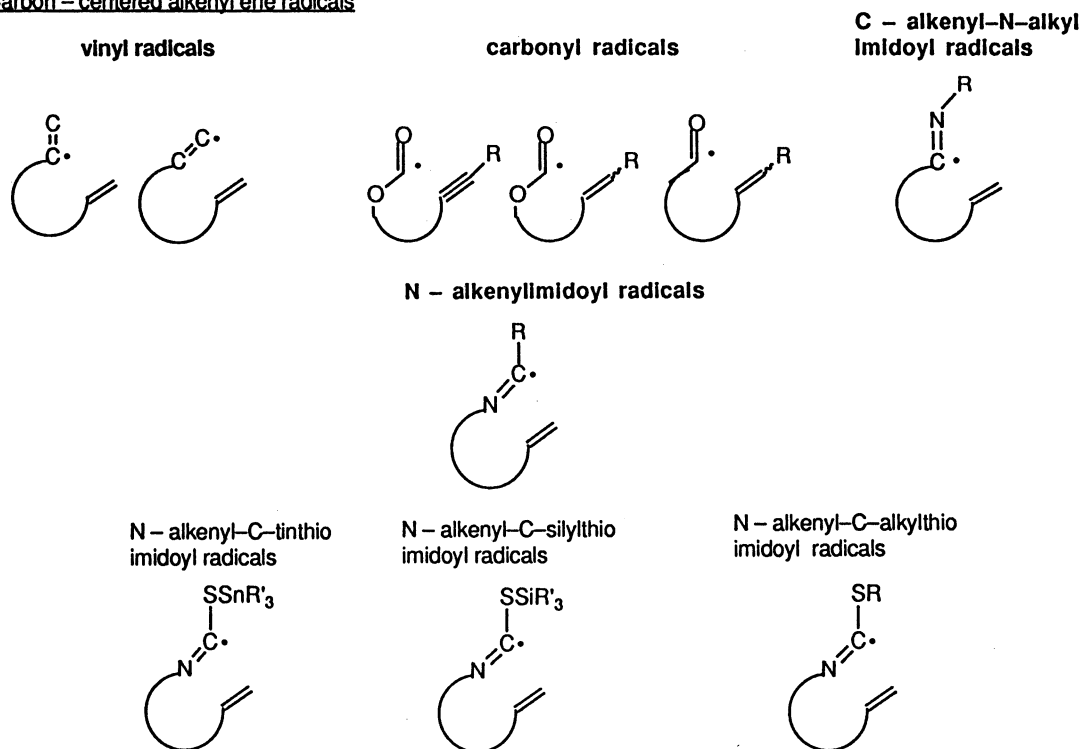
Scheme 9



In summary, free radical annelations based on the intramolecular addition of carbon centered ene radicals to carbon-carbon multiple bonds are useful for the synthesis of γ - and δ -lactones thiolactones, lactams, and thiolactams, substituted pyrrolines, and chromanones. General structures of carbon-centered ene radicals are shown in Scheme 10. The carbonyl radicals and imidoyl radicals discussed in this report are isoelectronic to the vinyl radicals introduced by Stork for the synthesis of cyclic compounds,¹⁹ and exhibit a similar chemistry. The carbon-centered imidoyl radicals are subdivided into C-alkenyl-N-alkyl(or aryl)imidoyl radicals and N-alkenylimidoyl radicals. Of the latter group, reactions involving tinthioimidoyl-, silylthioimidoyl-, alkylthioimidoyl-, and arylthioimidoyl- radicals were described.

Scheme 10

Carbon – centered alkenyl ene radicals



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