Tetrahedron Vol 46, No. 7, pp. 2317–2328, 1990
Printed in Great Britain

0040-4020/90 $3.00 + .00

N-HYDROXYPYRIDINE-2-THIONE CARBAMATES. IV. A COMPARISON OF 5-*EXO* CYCLIZATIONS OF AN AMINYL RADICAL AND AN AMINIUM CATION RADICAL

Martin Newcomb*, Thomas M. Deeb and Donald J. Marquardt

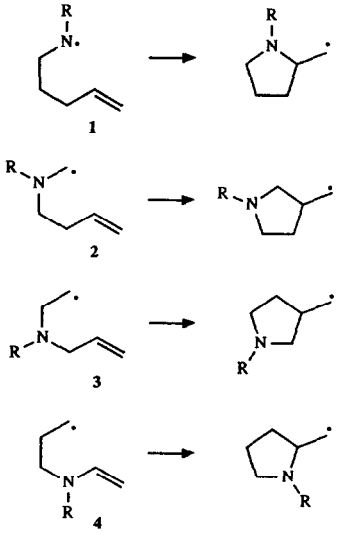
Department of Chemistry, Texas A&M University, College Station, Texas, 77843, USA

(*Received in USA* 6 *December* 1989)

Abstract: Cyclizations of the *N*-butyl-4-pentenaminyl radical and the *N*-butyl-4-pentenaminium cation radical were studied. The radicals were produced in chain reactions from the same *N*-hydroxypyridine-2-thione carbamate precursor. Rate constants for cyclization of the aminyl radical and ring opening of the product thus formed at 50 °C were determined. Cyclizations of the aminium cation radical, formed by protonation of the aminyl radical, were studied under a variety of conditions.

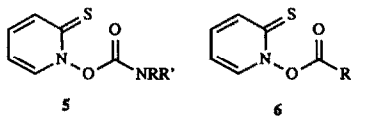
Free radical chemistry has recently enjoyed a considerable amount of attention from synthetic chemists.[1] One of the more useful classes of radical conversions for synthesis is the cyclization reaction represented by conversion of the 5-hexenyl radical to the cyclopentylmethyl radical, and various such cyclizations have been incorporated into complex synthetic constructions. The 5-hexenyl radical cyclization also has been extended to the production of heterocyclic rings, and, although the heterocyclic ring forming reactions are less well characterized than their carbocyclic counterparts, examples of pyrrolidine formation by cyclizations of several nitrogen-containing radicals have been reported. Thus, 1-aza-5-hexenyl (**1**),[2,3] 2-aza-5-hexenyl (**2**),[4] 3-aza-5-hexenyl (**3**)[4d,5] and 4-aza-5-hexenyl (**4**)[6] radicals can cyclize when appropriate substitution is present on the olefinic portion of the radical.

For radical **1** the nitrogen atom can be neutral (an aminyl radical) or protonated or complexed with a Lewis acid (an aminium cation radical). Often the distinction between aminyl and aminium radicals has not been clear, but it is important. The nature of the radicals changes from "nucleophilic" to "electrophilic" upon protonation, and the reactivity in terms of additions to unsubstituted olefins is greater for aminium cation radicals.[7] In this paper we report details of the simple pyrrolidine forming reaction represented by the cyclization of **1**. Cyclizations of both an aminyl radical and an aminium cation radical have been studied. Our model reaction was cyclization of the *N*-butyl-5-pentenaminyl system in part due to the fact that several previous reports of results with this and closely related systems are available for comparisons. Accompanying papers describe extensions of this chemistry to the production of a variety of heterocyclic skeletons by aminium cation radical cyclizations and studies aimed at developing useful carbon radical functionalization reactions subsequent to the cyclization reaction.



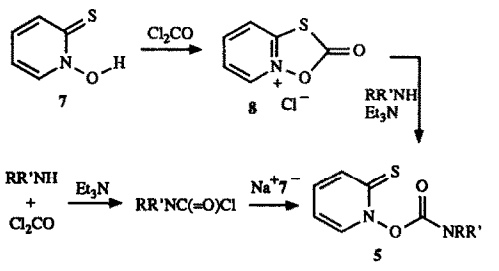
N-Hydroxypyridine-2-thione Carbamates

The radical precursors used in this work and in the subsequent papers were *N*-hydroxypyridine-2-thione carbamates (**5**), actually mixed anhydrides of a carbamic acid and a thiohydroxamic acid. Compounds **5** are related to Barton's *N*-hydroxypyridine-2-thione esters (**6**). For convenience, the acronym PTOC (for pyridine-2-thioneoxycarbonyl) can be employed. The PTOC esters are useful radical precursors for synthetic conversions[8,9] and for kinetic studies[10] for a variety of reasons, and the PTOC carbamates exhibit many of the features of their ester counterparts.



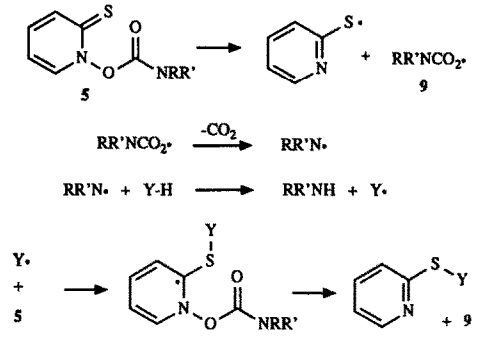
5 6

Scheme 1



7 8 5

Scheme 2



5 9

PTOC carbamates are readily prepared by the two routes shown in Scheme 1. The more convenient route involves the use of salt **8** which is prepared from commercially available *N*-hydroxypyridine-2-thione (**7**) and phosgene.[8] Salt **8** can be prepared *in situ*, or it can be isolated and used as a reagent; it has an extended shelf life when kept dry with no noticeable decomposition over at least several months. The reaction of **8** with secondary amines in the presence of Et_3N gives carbamates **5** in good to excellent yields.[11] Alternatively, a dialkylamine can be added to phosgene to produce a carbamoyl chloride that will react with the sodium salt of **7** to give carbamate **5**.[11]

Like esters **6**, carbamates **5** are yellow, photosensitive compounds. Generally, they are stable upon storage at room temperature in bottles shielded from light. They can be purified by recrystallization or chromatography on silica gel (with partial decomposition). In principle, carbamates **5** could be formed *in situ* and used without purification, but we have not used that expediency.

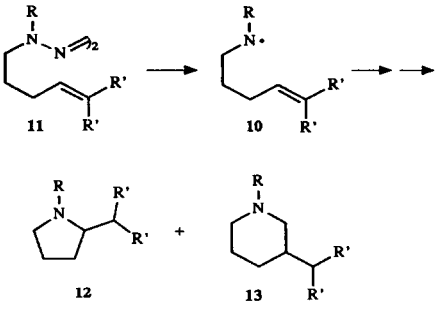
Carbamates **5** react in a radical chain reaction sequence that is similar to that for reactions of PTOC esters **6** (Scheme 2). Visible irradiation from a simple tungsten filament lamp initiates the chain reaction by homolysis of the weak N–O bond. The carbamoyloxy radical (**9**) shown in the scheme is probably a discrete intermediate, but it decarboxylates quite rapidly to give the aminyl radical; attempts to detect carbamoyloxy radicals by laser flash methods have not been successful.[12] In the presence of a good hydrogen atom donor, Y–H, the aminyl radical will be reduced to an amine, and the resulting radical Y• thus formed will add to the PTOC carbamate precursor in another chain propagation step. The addition product is a likely intermediate that has not been detected. One important difference between PTOC carbamates **5** and PTOC esters **6** is that

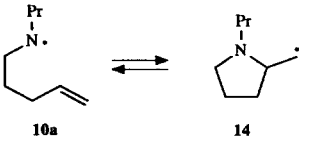
the dialkylaminyl radical will not add to the PTOC carbamate[13] whereas an alkyl radical will add readily to both PTOC esters and carbamates.

Aminyl Radical Cyclization

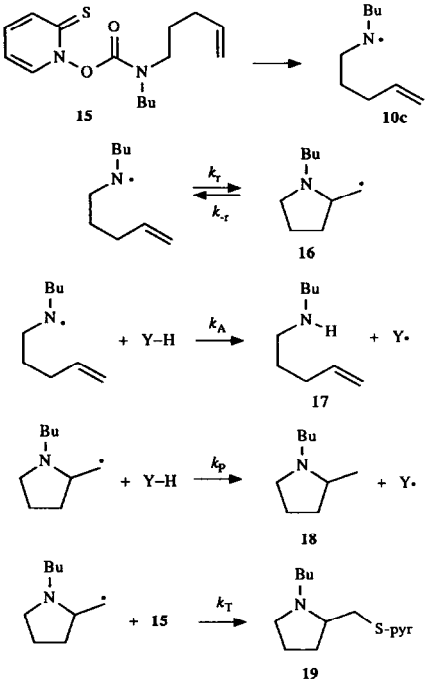
Michedja and co-workers reported[2c] that the *N*-propyl-4-pentenaminyl radical (**10a**), formed from the corresponding symmetrical tetrazene (**11a**) by photolysis at 23 °C or thermolysis at 140 °C, cyclized to produce, ultimately, pyrrolidine **12a** and piperidine **13a** in about 55% combined yields. It is possible that an error was made in the identification of piperidine **13a** because the 5-*exo* product is strongly favored over the 6-*endo* product in cyclizations of 5-hexenyl radicals,[14] and we have not observed piperidine products in measurable yields from aminyl radicals related to **10**. However, pyrrolidine **12a** undoubtedly was produced. In a directly analogous set of reactions, tetrazene **11b** was decomposed thermally and photochemically to give radical **10b** that gave, ultimately, pyrrolidine **12b** and an oxidized analog in combined yields of 24-39%.[15]

When Ingold and Maeda attempted to study the cyclization of radical **10a** by ESR spectroscopy, however, they were unable to detect the cyclic, carbon-centered radical **14**, and they estimated an upper limit for the rate constant for cyclization of **10a** to be 5 s^{-1} at 25 °C.[16] Such a slow cyclization reaction rate is not consistent with the formation of appreciable amounts of cyclized products from **10a** because radical disproportionation reactions would be expected to compete with diffusion controlled rate constants. A simple calculation shows that, with a rate constant for cyclization of **10a** of 5 s^{-1}, a 50% yield of cyclic products can only result if the total radical concentration remained less than 1 x 10^{-9} M. This, in turn, would require a total reaction velocity of less than 1 x 10^{-8} M s^{-1} or (assuming zero order kinetics) a reaction period for an initially 0.1 M solution of **11a** of several months.[17] The apparent dichotomy is resolved if (1) the cycliza-





Scheme 3



tion or the aminyl radical **10a** is more rapid than Ingold and Maeda estimated and (2) the cyclization reaction is reversible with the aminyl radical favored at equilibrium.

In order to study an aminyl radical cyclization under mildly reductive conditions, PTOC carbamate **15** was allowed to react at 50 °C in radical chain reactions in the presence of various hydrogen atom donors. Products were identified by GC, and the yields are given in Table 1. The reactions in Scheme 3 are important. Radical **10c** can cyclize to radical **16** or react with the hydrogen atom donor (Y–H) to give amine **17**. Cyclic radical **16** can also react with Y–H to give pyrrolidine **18**, or it can react with precursor **15** to give the pyridylthio-substituted product **19**. If our hypothesis is correct, radical **16** also can ring open to give **10c**.

As the data in Table 1 shows, the reactive hydrogen atom donor *t*-BuSH[18] intercepted aminyl radical **10c** efficiently even at the low concentration employed. In the presence of the less reactive hydrogen atom donor Bu_3SnH,[18] aminyl radical **10c** cyclized in competition with the hydrogen atom transfer reaction; the change in product ratios as a function of the concentration of trapping agent is analyzed below. When Ph_3SiH was used as trapping agent, the product ratio was constant suggesting that an equilibration between radicals **10c** and **16** was faster than the trapping reactions. A rapid radical equilibration relative to trapping also is suggested in the Et_3SiH reactions, but in this case the hydrogen atom donor was so poor that reaction of cyclic carbon-centered radical **16** with precursor **15** was faster than the reaction of **16** with the silane.

The ratio of amine **17** to pyrrolidine **18** found in the Bu_3SnH trapping studies is plotted as a function of tin hydride concentration in Figure 1. There is scatter in the data, but the intercept of the plot appears to be greater than zero indicating that the ring opening reaction of radical **16** competed with trapping by Bu_3SnH. The rate law for formation of amine **17** is given in eq 1, and a steady state assumption for the concentration of cyclic radical **16** results in the rate law for formation of pyrrolidine **18** given in eq 2.

Table 1. Products from Reactions of PTOC Carbamate 15 in the Presence of Hydrogen Atom Donors[a]

Donor	Conc. (M)	Relative % Yield			Total %
		17	**18**	**19**	Yield
t-BuSH[b]	0.02	100			80
Bu_3SnH	0.10	81	19		85
	0.104	73	27		65
	0.204	90	10		85
	0.25	90	10		90
	0.52	93	6		75
	0.76	95	5		75
	0.94	96	4		38
	1.02	100	<1		81
Ph_3SiH	[c]	37	63	[d]	74
Et_3SiH	0.1	67	<1	33	48
	0.5	67	<1	33	66
	1.0	45	7	48	76

[a]Conditions: benzene solvent, 50 °C, 0.01 M **15**. Product Yields were determined by GC using an internal standard. [b]0.004 M **15**. [c]Average of 10 runs at concentrations between 0.11 and 1.12 M; the range of the relative yields was ± 5%. [d]Product **19** was detected, but GC quantitation was precluded by the large peak from Ph_3SiH.

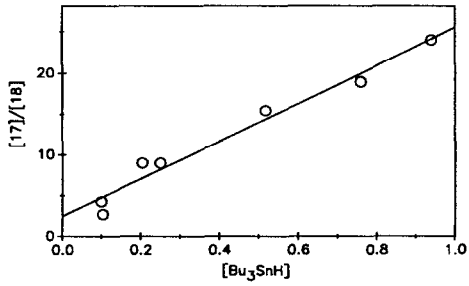


Figure 1. Data from Table 1. The slope is (23 ± 2) M^{-1}, and the intercept is (2.4 ± 1).

Division, integration and rearrangement gives the integrated competition rate law in eq 3. The rate constants in these equations are for the reactions shown in Scheme 3.

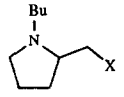
$$d[\mathbf{17}]/dt = k_A[\mathbf{10c}][Bu_3SnH] \quad (1)$$

$$d[\mathbf{18}]/dt = k_p k_r[\mathbf{10c}][Bu_3SnH](k_{-r} + k_p[Bu_3SnH])^{-1} \quad (2)$$

$$[\mathbf{17}]/[\mathbf{18}] = (k_A k_{-r})(k_p k_r)^{-1} + (k_A/k_r)[Bu_3SnH] \quad (3)$$

Because a large excess of Bu_3SnH was used in all of the reactions, the concentration of the tin hydride can be taken as a constant. From the slope of the function shown in Figure 1 (23 M^{-1}) and the approximate rate constant for reaction of Bu_3SnH with $R_2N\bullet$ at 50 °C,[18] the calculated rate constant for the cyclization of **10c** at 50 °C is (3.5 ± 0.3) x 10^3 s^{-1}. A crude value for the rate constant for ring opening of radical **16** results by dividing the intercept by the slope to factor out the (k_A/k_r) term and using 3.9 x 10^6 M^{-1} s^{-1} for the rate constant for reaction of a primary radical with Bu_3SnH at 50 °C.[19] The rate constant k_{-r} obtained from this approach is in the range of 10^5 s^{-1}, but, given the large error in the intercept, this value is not reliable.

A somewhat more precise value for k_{-r} for radical **16** could be determined by generating this radical directly. Attempts to produce radical **16** by reactions of *N*-butyl-2-(chloromethyl)pyrrolidine (**20a**) in the presence of Bu_3SnH were thwarted by the instability of the nitrogen mustard which is known[20] to rearrange and the relatively high temperatures required to initiate radical chain reductions of alkyl halides by the tin hydride. As an alternative, the selenide **20b** was employed as the radical source.



20a: X = Cl
b: X = SePh

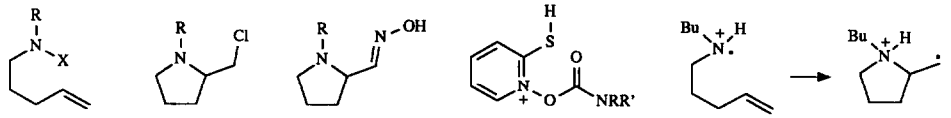
Treatment of **20b** with Bu_3SnH in benzene at 50 °C resulted in reduction of **20b**. However, due to the rapid reaction of the carbon radical with Bu_3SnH, low concentrations of the tin hydride were required to give detectable amounts of amine **17**, and the maximum amount of **17** detected in any reaction was only 4%. Nevertheless, reductions of **20b** with 0.021, 0.045 and 0.10 M Bu_3SnH (mean concentrations) gave **18/17** in ratios of 19, 32 and 49, respectively, and in total yields of 80-90% as determined by GC. These ratios were fit to eq 4 which results from a steady state treatment for radical **10c** and where $[Bu_3SnH]_m$ is the mean concentration of the tin hydride. The value for (k_p/k_{-r}) of 370 ± 50 M (1 σ) combined with the rate constant of 3.9 x 10^6 M^{-1} s^{-1} for reaction of Bu_3SnH with a primary radical at 50 °C, gave a value for k_{-r} at 50 °C of (1.0 ± 0.1) x 10^4 s^{-1}.

$$[\mathbf{18}]/[\mathbf{17}] = (k_p k_r)(k_A k_{-r})^{-1} + (k_p/k_{-r})[Bu_3SnH]_m \quad (4)$$

From the values of k_r and k_{-r}, the equilibrium constant for the cyclization of radical **10c** to radical **16** at 50 °C is about 0.35.[21] Not only is the rate of cyclization of the neutral aminyl radical slow in comparison to that of its carbon analog 5-hexenyl radical, but also the acyclic aminyl radical **10c** is energetically favored over cyclic radical **16**.[22]

As we anticipated above, the equilibration between aminyl radical **10c** and cyclic radical **16** with **10c** favored readily accounts for Ingold and Maeda's inability to detect a cyclic radical in their ESR studies of **10a**.[16] More importantly for synthetic applications, however, our kinetic results show that neutral aminyl radicals will be of limited utility due to the lack of reactivity of these radicals unless one carefully controls reaction conditions. In the case of an intramolecular reaction with an unactivated site like the cyclization reaction of **10c**, one might be able to offset the effects of the unfavorable equilibrium by the use of trapping

agents that react with carbon radicals much faster than they react with aminyl radicals.[24] However, the rate of the cyclization reaction will be a problem even if such trapping agents are employed. With a relatively slow rate limiting step in a radical chain sequence, one is required to control conditions precisely to avoid unwanted radical disproportionation reactions that occur with diffusion limited rate constants.[25] Intramolecular aminyl radical additions to electron deficient olefins might prove to be more useful both due to faster reaction rates and an equilibrium more favorable for the stabilized radical formed by the addition.



21a: X = Cl
b: X = NO

22 **23** **24** **25** **26**

Aminium Cation Radical Cyclization

Despite the fact that simple δ,ε-unsaturated aminyl radicals like **10c** cyclize only slowly, successful cyclizations of analogous aminium cation radicals are known. The most extensive investigations of these reactions have been conducted by Surzur's group which has reported many variations of the archetypal reaction represented by the conversion of chloramine **21a** to pyrrolidine **22**.[2a,b] Generally, these reactions were conducted under strongly acidic conditions such as H_2SO_4 in acetic acid, or with Lewis acids such as $TiCl_3$ in place of the Brønsted acids. δ,ε-Unsaturated-*N*-nitrosamines (**21b**) similarly react in the presence of acids with photochemical initiation to give, ultimately, oximes **23**.[2f]

Strong acids are not required to protonate dialkylaminyl radicals, however. Fessenden and Neta determined by ESR methods that the pK_a of dimethylaminium cation radical is about 7.[26] Therefore, it was conceivable that PTOC carbamates in the presence of weak acids could be used as sources of aminium cation radicals, and this has proven to be possible. The strength of the acid and the medium are important variables, however. If the conditions are not acidic enough, the aminyl radical will, of course, not be protonated, but, if the reaction mixture is too strongly acidic, the PTOC carbamates will be protonated. For example, dissolution of the simple dipropyl PTOC carbamate (**5**, R = R' = propyl) in neat CF_3CO_2H resulted in a complete loss of the long wavelength band responsible for the yellow color of the compound, but the PTOC carbamate was reisolated after the mixture was treated with base.[27] We presume that protonation occurred on sulfur to give the thiol cation **24**.

In a preliminary communication, we reported that when PTOC carbamate **15** was allowed to react in benzene at 25 °C in the presence of acetic acid and *t*-BuSH, good yields of pyrrolidine **18** could be obtained in addition to some acyclic amine **17**.[3] Pyrrolidine **18** was the major product even when the *t*-BuSH concentration was high. These results, combined with the observation that no cyclic product was found when **15** reacted in the presence of 0.02 M *t*-BuSH in the absence of acid, require that the aminyl radical **10c** was protonated and that aminium cation radical **25** was the species that cyclized to give radical **26**. However, acetic acid did not completely protonate aminyl radical **10c**; in a dilute benzene solution containing the stronger acid CF_3CO_2H in the presence of *t*-BuSH, PTOC carbamate **15** gave no acyclic amine **17**.[3]

In organic solvents, the identity of both the acid and the solvent should be important in determining the extent of protonation of the aminyl radical; increasing the solvent dielectric constant would be expected to result in more complete protonation for a given acid. Thus, we have determined the product distributions

from reactions of carbamate **15** in the presence of *t*-BuSH while varying both the acid source and the solvent. The objective of these experiments was to determine the conditions most favorable for cyclization; low concentrations of both the acid and *t*-BuSH were used, and cyclic sulfide **19** (resulting from the PTOC carbamate self-trapping reaction) was produced in addition to amine **17** and pyrrolidine **18**. The results are collected in Table 2.

It is apparent that acetic acid did not protonate the aminyl radical completely and that the stronger malonic acid protonated the aminyl radical to a much greater extent. In acetonitrile, malonic acid appears to have protonated the aminyl radical completely. Highly variable results were found when CF_3CO_2H was employed as the acid; we suspect that this was caused by partial protonation of the PTOC carbamate precursor to give cation **24** which should act as a hydrogen atom donor and is unlikely to participate in the desired radical chain propagation step. Reactions in the hydroxylic solvent methanol were attempted, but these resulted in complex product mixtures. We speculate that the PTOC carbamate reacted with methanol under the acidic conditions. From the results in Table 2, acetonitrile is the solvent of choice for cyclizations of **25**.

Table 2. Products from Reactions of PTOC Carbamate 15 in the Presence of Acids and *t*-BuSH[a]

Solvent	Acid	Relative % Yield			Total %
		17	**18**	**19**	Yield
benzene[b]	CH_3CO_2H	97	2	1	91
THF[b]		94	4	3	99
CH_3CN		49	36	15	98
benzene[c]	$CH_2(CO_2H)_2$	100			98
THF		31	39	30	97
CH_3CN			43	57	100
benzene[d]	CF_3CO_2H	8	23	69	87
CH_3CN[d]		4	33	62	90

[a]Conditions: 25 °C, 0.05 M **15**, 0.07 M t-BuSH, 0.15 M acid. Product Yields were determined by GC using an internal standard. The yields are the averages of several runs. [b]Higher yields of cyclic products were obtained at higher dilutions. [c]Malonic acid was not noticeably soluble in benzene. [d]The acid concentration was 0.07 or 0.15 M; these reactions gave highly variable results.

Table 3. Products from Reactions of PTOC Carbamate 15 in the Presence of Acids[a]

Solvent	Acid	Relative % Yield			Total %
		17	**18**	**19**	Yield
benzene	CH_3CO_2H	19		81	69
CH_3CN		15	1	84	69
benzene	$CH_2(CO_2H)_2$			100	97
THF				100	96
CH_3CN				100	98
benzene	CF_3CO_2H	6		94	85

[a]Conditions: 25 °C, 0.05 M **15**, 0.15 M acid. Product Yields were determined by GC using an internal standard. The yields are the averages of several runs.

Reactions of precursor **15** under acidic conditions but in the absence of a hydrogen atom donor also were studied (Table 3). Sulfide **19** was the predominant product, and some acyclic amine **17** was produced, probably by radical disproportionation reactions, when acetic acid was employed. These results are generally consistent with those found when *t*-BuSH was present. Except for the presence of the thiol, the reactions in Table 3 were run under the same conditions as those in Table 2. The increased yields of cyclic products in the absence of thiol for otherwise similar reactions resulted because the nitrogen-centered radicals do not react with the PTOC precursors,[11] and protonation and cyclization were essentially the only viable reaction channels. This feature was used to drive cyclizations in the following paper.

Table 4. Effects of Hydrogen Atom Donors on Reactions of PTOC Carbamate 15 in the Presence of Malonic Acid[a]

Donor	Conc. (M)[b]	Relative % Yield			Total % Yield	k_r/k_H[c]	k_H/k_T[d]
		17	**18**	**19**			
t-BuSH	0.07		43	57	100		0.4
	0.28		74	26	96		0.3
	0.70		87	13	95		0.2_5
	2.20		95	5	97		0.2
Bu_3SnH	0.07	12	73	15	82	0.33	3
	0.28	41	56	3	86	0.37	2
	0.70	67	33	<1	85	0.33	

[a]Conditions: 25 °C, acetonitrile solvent, 0.05 M **15**, 0.15 M malonic acid. Product yields were determined by GC using an internal standard. The yields are the averages of several runs. [b]Initial concentration of hydrogen donor. [c]From equation 5. [d]From equation 6.

Tributyltin hydride could be used as the hydrogen atom donor in place of *t*-BuSH. The results of a series of experiments that permits a direct comparison of the effects of the two hydrogen atom donors are collected in Table 4. The most remarkable feature of these results is that Bu_3SnH was clearly a better trapping agent than *t*-BuSH for both the aminium cation radical **25** and the cyclic radical **26**. This is just the opposite effect as that seen for reactions of these two hydrogen atom donors with both neutral aminyl radicals[18] and simple alkyl radicals.[28] It is likely that this dramatic reversal in reactivity is due to the "electrophilic" nature of the positively charged radicals **25** and **26** and the polarizations of the bonds to hydrogen in the two donors.

Given that the neutral aminyl radical **10c** was efficiently trapped by *t*-BuSH at low concentrations (Table 1) and that no acyclic amine was detected when high concentrations of *t*-BuSH were employed in the studies collected in Table 4, one concludes that protonation to give the aminium cation radical **25** was essentially complete in the latter studies. With the assumption that cyclization of **25** in the presence of Bu_3SnH was effectively irreversible, the relative rate constants for cyclization (k_r) and trapping of **25** by Bu_3SnH (k_H) at 25 °C are given by eq 5 where $[Bu_3SnH]_m$ is the mean concentration of tin hydride. The values for k_r/k_H for each reaction are given in Table 4. That the same ratio of rate constants was found when the mean concentration of tin hydride was varied by a factor of 15 confirms that the cyclization reaction was irreversible. The relative rate constants cannot be further evaluated without some absolute rate constants for reactions of aminium cation radicals, but it is interesting to note that the cyclization of the charged radical **25** relative to Bu_3SnH trapping was about an order of magnitude more efficient than cyclization of the neutral aminyl radical **10c** relative to Bu_3SnH trapping (at 50 °C, $k_r/k_H = (23\ M^{-1})^{-1} = 0.043$ M).

$$k_r/k_H = ([\mathbf{18}]+[\mathbf{19}])([\mathbf{17}])^{-1}[Bu_3SnH]_m \quad (5)$$

$$k_H/k_T = ([\mathbf{18}]/[\mathbf{19}])(0.025M/[Y\text{–}H]_m) \quad (6)$$

Approximate ratios for the rate constants for reaction of cyclic radical **26** with the hydrogen atom donors (k_H) and with PTOC carbamate **15** (k_T) can be evaluated from eq 6 where 0.025 M is the mean

concentration of **15** and $[Y–H]_m$ is the mean concentration of the hydrogen atom donor.[31] The calculated values are given in Table 4. The relative rate constants for reactions of **26** with *t*-BuSH, Bu_3SnH and PTOC **15** at 25 °C are about 0.3:2:1. The effect of the electron deficient nature of radical **26** is apparent when one compares the above ratio with the rate constants for reactions of simple primary radicals with *t*-BuSH, Bu_3SnH and PTOC esters at 25 °C which give the ratio 8:2:1, respectively.[28,33] Because of the consistency between the relative rate constants for the Bu_3SnH and PTOC trapping reactions, it is tempting to ascribe the results predominantly to a reduction of the rate constant for reaction of *t*-BuSH with the charged radical **26**; however, this is probably an oversimplification. As with Bu_3SnH, the polarity of the C–S bond in the PTOC carbamate would be expected to enhance its reactivity with electrophilic radicals, and we have found that PTOC carbamate self-trapping reactions of radicals like **26** appear to be unusually efficient in competition with a variety of other trapping agents.[23]

Conclusions. PTOC carbamates are useful precursors for both neutral dialkylaminyl radicals and dialkylaminium cation radicals, but for simple 5-*exo* cyclization reactions involving an unactivated olefin, the aminium cation radicals are superior intermediates. Although reactions with PTOC carbamates under acidic conditions can be conducted in a variety of non-hydroxylic solvents, the higher polarity solvent acetonitrile gives better results, and a mixed solvent such as THF–acetonitrile should be equally useful if precursor solubilities are a problem. The acid used for protonation of the dialkylaminyl radical is a critical variable; for the pyrrolidine forming reaction we have studied in this work, malonic acid was clearly the best choice, but we have found that acetic acid is adequate in other cases.[36]

Experimental Section

General. Commercial reagents were obtained from Aldrich Chemical Co. and used as obtained unless noted. ^1H and ^{13}C NMR spectra were obtained at 200 and 50 MHz, respectively, on various instruments; spectra of $CDCl_3$ solutions were recorded, and chemical shifts are reported in ppm downfield from internal Me_4Si. GC analyses were performed on instruments equipped with flame ionization detectors; capillary columns (0.25 mm) were used for compound identifications, and large bore capillary columns (0.52 mm) were used for quantitative analyses. GC mass spectral analyses were performed on a Hewlett-Packard (HP) 5790 GC interfaced to an HP 5970A mass selective detector using a low polarity capillary column (J&W Scientific, DB-1, 0.25 mm x 30 m). Radial chromatography was accomplished with a Chromatotron® model 7924T (Harrison Research). Analyses were preformed by Galbraith Laboratories.

***N*-Butyl-4-pentenamine (17)** was prepared by the method of Surzur[37] and by $LiAlH_4$ reduction of the corresponding butyramide. The amine was obtained as a clear oil in 80% yield: bp 110 °C (100 Torr) (lit.[37] bp 179 °C); ^1H NMR, δ 0.85 (t, 3 H), 1.0-1.7 (m, 7 H), 1.92-2.1 (m, 2 H), 2.4-2.6 (m, 4 H), 4.85-5.1 (m, 2 H), 5.69-5.9 (m, 1 H); ^{13}C NMR, δ 14.0, 20.5, 29.4, 31.6, 32.6, 49.6, 49.8, 114.4, 138.4; mass spectrum, *m/e* (intensity), 140 (2), 98 (100), 86 (94).

1[(Butyl(4-pentenyl)carbamoyl)oxy]-2(1H)-pyridinethione (15). *N*-Hydroxypyridine-2-thione (**7**) was precipitated from an aqueous solution of its sodium salt (Olin, sodium Omadine®) by addition of HCl. The precipitate was recrystallized from absolute ethanol to give **7** in 95% yield; mp 70-72 °C (lit.[38] mp 68-70 °C). Salt **8** was prepared from the reaction of **7** with phosgene by the method of Barton.[8] After drying in a vacuum desiccator over KOH, salt **8** had mp 115-116 °C (lit.[8] mp 108-110 °C).

PTOC carbamate **15** was prepared in several batches in yields ranging from 70 to 83% yield using Method A described in the accompanying paper.[36] In a typical reaction, 2.0 g (14.2 mmol) of amine **17** and 1.6 g of Et_3N in 20 mL of benzene was added to a suspension of 2.9 g (15.3 mmol) of salt **8** in 25 mL of benzene. Crude product **15** was dissolved in benzene, and the resulting solution was diluted with 5 volumes of hexane and cooled in an ice bath. Product **15** (3.1g, 10.5 mmol, 74%) crystallized. The mp of **15** varied depending on the heating rate, and decomposition was apparent in some cases; typical values were 79-82 (dec) and 83 °C. The NMR spectra were complicated by the presence of two conformers; thus, for example, two overlapping triplets

comprised an apparent quartet at δ 0.92 in the ^{1}H NMR spectrum, and the ^{13}C NMR spectrum contained more than 15 signals. ^{1}H NMR, δ 0.92 (q, 3 H), 1.32 (m, 2 H), 1.5-1.9 (m, 4 H), 2.08 (m, 2 H), 3.31 (t, 2 H), 3.47 (t, 2 H), 5.00 (m, 2 H), 5.78 (m, 1 H), 6.58 (dt, 1 H), 7.16 (dt, 1 H), 7.62 (m, 2 H); ^{13}C NMR, δ 13.95, 14.02, 20.10, 20.25, 26.79, 27.94, 29.79, 30.96, 31.16, 47.59, 47.98, 48.88, 49.22, 112.65, 112.77, 115.71, 115.85, 133.96, 137.69, 138.12, 139.28, 151.0, 175.7. *Anal.* Calcd for $C_{15}H_{22}N_2O_2S$: C, 61.19; H, 7.53. Found: C, 61.12; H, 7.37.

***N*-Butyl-2-methylpyrrolidine (18).** An authentic sample was prepared by butylation of 2-methylpyrrolidine under phase transfer conditions[39] (1-bromobutane, NaOH, benzyltrimethylammonium hydroxide, benzene, reflux, 12 h). The amine was obtained as a clear oil in ca. 75% yield: bp 103 °C (130 Torr) (lit.[39b] bp 67-74 °C (44 Torr)); ^{1}H NMR, δ 0.75 (t, 3 H), 0.9 (d, 3 H), 1.0-2.15 (m, 11 H), 2.5-2.7 (m, 1 H), 2.9-3.1 (m, 1 H); ^{13}C NMR, δ 13.9, 18.9, 20.9, 21.5, 30.9, 32.6, 53.9, 54.0, 60.0; mass spectrum, *m/e* (intensity), 141 (5), 126 (28), 98 (100), 70 (30).

***N*-Butylpiperidine.** An authentic sample was prepared by butylation of piperidine (as above). The amine was obtained as a clear oil in 80% yield: bp 50 °C (22 Torr) (lit.[39b] bp 47-49 °C (22 Torr)); ^{1}H NMR, δ 0.9 (t, 3 H), 1.2-1.6 (m, 10 H), 2.1-2.4 (m, 6 H); ^{13}C NMR, δ 13.4, 20.2, 24.4, 25.9 (2 C's), 29.0 (2 C's), 54.3, 59.0.

***N*-Butyl-2-[(2'-thiopyridyl)methyl]pyrrolidine (19)** was obtained from reactions of PTOC carbamate **15** as described in the accompanying paper.[36]

***N*-Butyl-2-[(phenylseleno)methyl]pyrrolidine (20b)** was prepared by the reaction of PTOC **15** in the presence of Ph_2Se_2[36] and by the method of Toshimitsu[40] by intramolecular amidoselenylation and reduction. The latter procedure is described below.

N-(4-Pentenyl)butyramide was prepared by the reaction of 4-pentenamine (0.83 g, 9.8 mmol) with excess butyric anhydride in 30 mL of THF containing 2.5 g of Et_3N (3 h, 25 °C). The amide was purified by chromatography (silica gel, 1:1 hexane--EtOAc) to give an 80% yield of the amide as an oil that was pure by NMR spectroscopy: ^{1}H NMR, δ 0.85 (t, 3 H), 1.2-1.7 (m, 4 H), 1.9 2.15 (m, 4 H), 3.2 (q, 2 H), 4.8-5.05 (m, 2 H), 5.6-5.85 (m, 1 H), 5.9-6.2 (broad s, 1 H); ^{13}C NMR, δ 13.6, 19.1, 28.6, 30.9, 38.4, 38.8, 114.9, 137.6, 173.1.

To a dry flask containing 50 mL of dry CH_3CN and 0.75 g (4.84 mmol) of the above amide was added dropwise a solution of 1.14 g (5.3 mmol) of PhSeBr in 5 mL of dry CH_3CN. The yellow solution was stirred for 12 h. Saturated aqueous $NaHCO_3$ solution (50 mL) was added, the phases were separated, and the aqueous phase was extracted with CH_2Cl_2 (5 x 50 mL). The combined organic phase was washed with saturated aqueous NaCl solution and dried with $MgSO_4$. Filtration and distillation of solvent gave crude *N*-Butyryl-2-[(phenylseleno)methyl]pyrrolidine contaminated with Ph_2Se_2. Purification by radial chromatography (silica gel, 3:1 hexanes--EtOAc) gave 1.50 g (76%) of the product. NMR spectra were complicated due to the presence of two conformers in a 3:1 ratio: ^{1}H NMR, δ 0.8 (t, 0.75 H), 0.95 (t, 2.25 H), 1.4-1.75 (m, 2 H), 1.8-2.05 (m, 5 H), 2.0-2.2 (m, 1 H), 2.70 (dd, 0.25 H), 2.85 (dd, 0.75 H), 3.3-3.55 (m, 3 H), 3.8-4.0 (m, 0.25 H), 4.2-4.4 (m, 0.75 H), 7.2-7.3 (m, 3 H), 7.5-7.6 (m, 2 H); ^{13}C NMR (of the major isomer), δ 14.0, 18.2, 24.0, 29.6, 29.7, 36.9, 47.5, 56.9, 126.1, 131.4 (2 C's), 134.3 (2 C's), 171.9; mass spectrum, *m/e* (intensity), 310 (1), 267 (34), 191 (3), 159 (60), 140 (16), 70 (100).

The above amide (0.5 g, 1.61 mmol) was dissolved in 5 mL of dry ether, and the resulting solution was added to a flask containing 0.245 g (6.44 mmol) of $LiAlH_4$ and 20 mL of dry ether. After 6 h, the reaction mixture was treated successively with water (0.2 mL), 15% aqueous NaOH solution (0.2 mL) and water (0.7 mL). After stirring for 2 h, the mixture was filtered, and the filtrant was washed with dry ether. Solvent was distilled from the combined ethereal phase to give crude product **20b** that was purified by radial chromatography (alumina, hexane) to give 0.37 g (77%) of **20b** that was pure by NMR spectroscopy: ^{1}H NMR, δ 0.9 (t, 3 H), 1.2-1.5 (m, 5 H), 1.6-1.8 (m, 3 H), 1.8-2.2 (m, 3 H), 2.5-2.7 (m, 2 H), 2.9-3.2 (m, 2 H), 7.2-7.3 (m, 3 H), 7.4-7.5 (m, 2 H); ^{13}C NMR, δ 14.1, 20.8, 22.4, 30.9, 31.0, 33.2, 54.3, 54.5, 64.0, 126.5, 128.9, 130.3 (2 C's), 132.2 (2 C's).

Reactions of PTOC carbamate 15 in the absence of acids. PTOC carbamate **15** was weighed into a 5-mL volumetric flask (ca. 30 mg), and pentadecane (ca. 8 mg) was added as an internal standard. The vessel was sealed with a septum and flushed with N_2. The vessel was wrapped in aluminum foil, and dry benzene was degassed (several freeze-thaw cycles) and added to the volumetric flask to the mark. One mL of the above solution was added to several shielded, septum-sealed 2-mL volumetric flasks under nitrogen via syringe; the flasks contained a small stirring bar. The appropriate amount of *t*-BuSH, Bu_3SnH, Ph_3SiH or Et_3SiH was added to each flask, and benzene was added to the mark. The vessels were placed in a constant temperature bath at (50 ± 1) °C. After 5 min, the shields were removed, and (with stirring) the vessels were irradiated with a 100 W, tungsten filament lamp at a distance of about 0.3 m. PTOC carbamate was monitored by TLC. When the reactions were complete, the product mixtures were analyzed by GC and GC-mass spectrometry. Products **17**, **18** and **19** were identified by their GC retention times and mass spectral fragmentation patterns that matched those of the authentic samples. *N*-Butylpiperidine was shown not to be a product by GC comparison to the authentic sample. Product yields were quantified by GC; the response factors for **17**, **18** and **19** were determined independently using the authentic samples.

Reactions of PTOC carbamate 15 in the presence of acids. A 0.10 M stock solution of **15** containing 9-11 mg of pentadecane was prepared in the appropriate degassed solvent in a flask shielded from light. Reaction vessels, 10-cm test tubes equipped with small stir bars and sealed with septa, were flushed with N_2. The appropriate acid was added to the reaction vessel by syringe (solid malonic acid was added before the vessel was sealed) followed by degassed solvent to bring the volume to that necessary to reach 1 mL upon addition of the appropriate amount of reducing agent. To each reaction vessel was added 1 mL of the stock solution of **15** and the appropriate amount of *t*-BuSH or Bu_3SnH. The reaction vessels were placed in a bath at 25 °C and (with stirring) were irradiated with a 150 W, tungsten filament lamp at a distance of 0.6 to 0.9 m. The reactions were monitored by TLC for loss of **15** (ca. 10-20 min). After the reactions were complete, 0.1 mL of 20% aqueous NaOH solution was added, and the mixtures were stirred for several min. For reactions in benzene, the aqueous phase that separated was removed. Anhydrous K_2CO_3 was added, and the reaction mixtures were briefly stirred with a vortex stirrer. After standing for 1-2 h, the mixtures were centrifuged, and the solution was decanted from the solid. The reaction mixtures were analyzed by GC as described above.

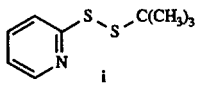
Reactions of selenide 20b were conducted by the method used for PTOC carbamate **15** in the absence of acids with the exception that the reaction vessels were not irradiated. No initiator was employed in these Bu_3SnH reactions. The reactions were monitored for loss of **20b** by TLC. Products were analyzed by GC as described above.

Acknowledgment. We thank the National Institutes of Health (GM 39303) and the Robert A. Welch Foundation for financial support.

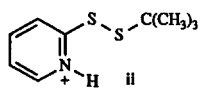
References and Notes

1. Giese, B. *Radicals in Organic Synthesis: Formation of Carbon-Carbon Bonds*; Pergamon: Oxford, 1986. Curran, D. P. *Synthesis* **1988**, 417, 489. Ramaiah, M. *Tetrahedron* **1987**, *43*, 3541.
2. (a) Stella, L. *Angew. Chem., Int. Ed. Engl.* **1983**, *22*, 337. (b) Surzur, J.-M. In *Reactive Intermediates*, Abramovitch, R. A., Ed.; Plenum: New York, 1982; Vol. 2, Chapter 2. (c) Michejda, C. J.; Campbell, D. H.; Sieh, D. H.; Koepke, S. R. In *Organic Free Radicals*; Prior, W. A., Ed.; ACS Symposium Series 69, American Chemical Society: Washington, D.C., 1978, p. 292. (d) Broka, C. A.; Eng, K. K. *J. Org. Chem.* **1986**, *51*, 5043. (e) Tokuda, M.; Yamada, Y.; Takagi, T.; Suginome, H.; Furusaki, A. *Tetrahedron* **1987**, *43*, 281. (f) Chow, Y. L.; Perry, R. A.; Menon, B. C.; Chen, S. C. *Tetrahedron Lett.* **1971**, 1545.
3. Newcomb, M.; Deeb, T. M. *J. Am. Chem. Soc.* **1987**, *109*, 3163.
4. (a) Bachi, M. D.; Frolow, F.; Hoornaert, C. *J. Org. Chem.* **1983**, *48*, 1841. (b) Burnett, D. A.; Choi, J.-K.; Hart, D. J.; Tsai, Y.-M. *J. Am. Chem. Soc.* **1984**, *106*, 8201. (c) Hart, D. J.; Tsai, Y.-M. *J. Am. Chem. Soc.* **1984**, *106*, 8209. (d) Padwa, A.; Nimmesgern, H.; Wong, G. S. K. *J. Org. Chem.* **1985**, *50*, 5620. (e) Choi, J. K.; Ha, D.-C.; Hart, D. J.; Lee, C.-S.; Ramesh, S.; Wu, S. *J. Org. Chem.* **1989**, *54*, 279.
5. Knight, J.; Parsons, P. J.; Southgate, R. *J. Chem. Soc., Chem. Commun.* **1986**, 78. Barton, D. H. R.; Guilhem, J.; Hervé, Y.; Potier, P.; Thierry, J. *Tetrahedron Lett.* **1987**, *28*, 1413. Watanabe, Y.; Ueno, Y.; Tanaka, C.; Okawara, M.; Endo, T. *Tetrahedron Lett.* **1987**, *28*, 3953.
6. Beckwith, A. L. J; Westwood, S. W. *Tetrahedron* **1989**, *45*, 5269.
7. Neale, R. S. *Synthesis* **1971**, 1.
8. Barton, D. H. R.; Crich, D.; Motherwell, W. B. *Tetrahedron* **1985**, *41*, 3901.
9. Barton, D. H. R.; Zard, S. Z. *Pure Appl. Chem.* **1986**, *58*, 675.
10. Newcomb, M.; Park, S. U. *J. Am. Chem. Soc.* **1986**, *108*, 4132. Newcomb, M.; Glenn, A. G. *Ibid.* **1989**, *111*, 275.
11. Newcomb, M.; Park, S.-U.; Kaplan, J.; Marquardt, D. J. *Tetrahedron Lett.* **1985**, *26*, 5651.
12. Chateauneuf, J.; Lusztyk, J.; Maillard, B.; Ingold, K. U. *J. Am. Chem. Soc.* **1988**, *110*, 6727.
13. In the absence of trapping agents, the dipropylaminyl radical produced from **5** (R = R' = Pr) gave mainly dipropylamine and propylidenepropylamine from aminyl radical disproportionation.[11]
14. Beckwith, A. L. J.; Ingold, K. U. In *Rearrangements in Ground and Excited States*; de Mayo, P., Ed.; Academic: New York, 1980; Vol. 1, Essay 4.
15. Newcomb, M.; Burchill, M. T.; Deeb, T. M. *J. Am. Chem. Soc.* **1988**, *110*, 6528.
16. Maeda, Y.; Ingold, K. U. *J. Am. Chem. Soc.* **1980**, *102*, 328.
17. Based on a diffusion rate constant of $k_D = 2 \times 10^{10}$ M^{-1} s^{-1} and a spin statistical factor of 0.25 for radical–radical reactions; *cf.* Fischer, H.; Paul, H. *Acc. Chem. Res.* **1987**, *20*, 200.
18. Approximate rate constants for reactions of the hydrogen atom donors with $R_2N^{\bullet}$ at 50 °C are 2.5×10^6 M^{-1} s^{-1} for *t*-BuSH and 8×10^4 M^{-1} s^{-1} for Bu_3SnH.[11]
19. Johnston, L. J.; Lusztyk, J.; Wayner, D. D. M.; Abeywickreyma, A. N.; Beckwith, A. L. J.; Scaiano, J. C.; Ingold, K. U. *J. Am. Chem. Soc.* **1985**, *107*, 4594.

20. Paul, R.; Tchelitcheff, S. *Bull. Soc. Chim. Fr.* **1958**, 736. Brain, E. G.; Doyle, F. P.; Mehta, M. D. *J. Chem. Soc.* **1961**, 633.
21. The values for k_r and k_{-r} are in reasonable agreement with those reported for radical **10b** ($k_r = 3.3 \times 10^3$ s^{-1} and $k_{-r} \approx 8 \times 10^3$ s^{-1} at 50 °C).[15]
22. The reversible nature of the cyclization of radical **10c** was also apparent in attempted reductions of sulfide **19** with nickel reagents. Acyclic amine **17** was formed in addition to cyclic amine **18**, presumably from ring opening of the intermediate radical **16**.[23]
23. Newcomb, M.; Marquardt, D. J.; Kumar, M. U., accompanying paper in this issue.
24. Suginome *et al.*[2e] reported the formation of pyrrolidines in fair to good yields from the electrochemical oxidation of lithium dialkylamides containing δ,ε-unsaturation. Apparently, the carbon-centered radical is selectively trapped in these reactions.
25. For a radical chain reaction sequence with the slower, rate controlling step proceeding with a rate constant of 1000 s^{-1} at 25 °C in a typical organic solvent, a 50% loss of products to disproportionation would result if the radical concentration reaction 2×10^{-7} M. To obtain a 90% yield of a desired product, the radical concentration must remain below 2×10^{-8} M which would require that a reaction of 0.1 M substrate be conducted over a several hour time period.
26. Fessenden, R. W.; Neta, P. *J. Phys. Chem.* **1972**, *76*, 2857.
27. Newcomb, M.; Weber, K. A., unpublished results.
28. The rate constant for reaction of a simple primary radical with Bu_3SnH at 25 °C is 2.4×10^6 M^{-1} s^{-1},[19] and that for reaction with *t*-BuSH is 8.0×10^6 M^{-1} s^{-1}.[29]
29. Newcomb, M.; Glenn, A. G.; Manek, M. B. *J. Org. Chem.* **1989**, *54*, 4603.
30. Given the numerous applications of Bu_3SnH in synthesis, this observation could be generally important. It is possible that "electrophilic" radicals such as carbonyl stabilized radicals typically react faster with Bu_3SnH than one might expect based on considerations of radical stabilities. The *t*-butoxy radical reacts with Bu_3SnH with a rate constant of 2×10^8 M^{-1} s^{-1} at 27 °C (*cf.* Scaiano, J. C. *J. Am. Chem. Soc.* **1980**, *102*, 5399).
31. One possible explanation for the increased yield of sulfide **19** was that a new, reactive trapping agent was produced in the reaction medium. A by-product in the radical chain propagation sequence for the PTOC carbamate is disulfide **i** which should be protonated under our conditions to give cation **ii**. Disulfides are known to react with carbon radicals,[32] so trapping by these species was possible in principle. A simple control reaction showed that this reaction was not important; when excess disulfide **i** was added to a reaction mixture, there was no noticeable effect on the product distribution.



i



ii

32. Barton, D. H. R.; Bridon, D.; Zard, S. Z. *Heterocycles* **1987**, *25*, 449.
33. The rate constants for reactions of PTOC *esters* with simple primary alkyl radicals at 25 °C are ca. 1×10^6 M^{-1} s^{-1}.[34,35] We make the assumption that the PTOC carbamates studied here will react with about the same rate constants.
34. Newcomb, M.; Kaplan, J. *Tetrahedron Lett.* **1987**, *28*, 1615.
35. Newcomb, M.; Kaplan, J., unpublished results.
36. Newcomb, M.; Marquardt, D. J.; Deeb, T. M., accompanying paper in this issue.
37. Surzur, J.-M.; Stella, L.; Tordo, P. *Bull. Soc. Chim. Fr.* **1970**, 111.
38. Shaw, E.; Bernstein, J.; Losee, K.; Lott, W. A. *J. Am. Chem. Soc.* **1950**, *72*, 4362.
39. (a) Barco, A.; Benetti, S.; Pollini, G. P.; Baraldi, P. G. *Synthesis* **1976**, 124. (b) Burchill, M. T., Ph. D. Thesis, Texas A&M University, 1984.
40. Toshimitsu, A.; Terao, K.; Uemura, S. *J. Org. Chem.* **1986**, *51*, 1724.