

FACILE GENERATION OF DIALKYLAMINYL RADICALS FROM N-HYDROXYPYRIDINE-2-THIONE CARBAMATES.
APPLICATION IN KINETIC STUDIES OF SMALL RING CYCLOALKYLAMINYL RADICAL RING OPENINGS

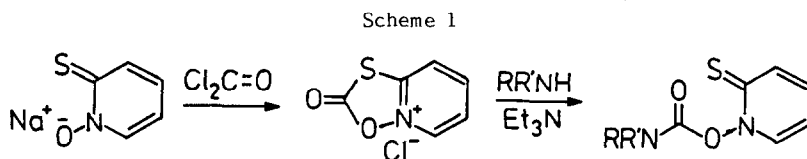
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Summary: The preparation of N-hydroxypyridine-2-thione carbamates and the formation of dialkylaminyl radicals from these species are described, and the application of this methodology in kinetic studies of aminyl radical rearrangements is demonstrated.

We have used aminyl radical rearrangements as probe reactions to detect the formation of aminyl radicals, and by inference electron transfer processes, in reactions of lithium dialkylamides with various organic oxidants.² Although we could confirm qualitatively that aminyl radical rearrangements would be expected in our probe substrates by generating the aminyl radicals from tetrazenes,³ this method was poorly suited for kinetic studies, and the only measured rate of rearrangement of an aminyl radical is that reported by Ingold and Maeda for the ring opening of a cyclobutylaminyl radical.⁴ The recent methodology developed by Barton⁵ for facile generation of carbon radicals appeared to be well suited for the generation of aminyl radicals under mild, controlled conditions. Herein we report that that methodology can be extended to the generation of aminyl radicals. The aminyl radicals thus formed can be used in kinetic studies, and, in light of the recent increase in interest in the use of radicals in organic synthesis, should have synthetic applications.⁶

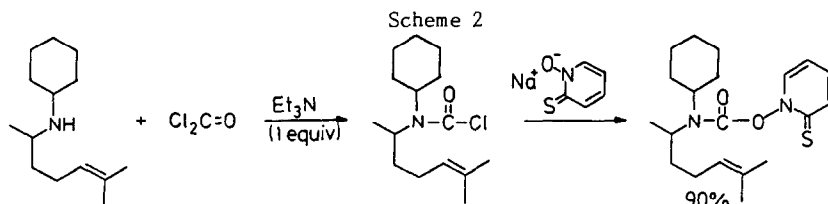


Barton's method for controlled generation of carbon radicals employs species like N-hydroxypyridine-2-thione esters (**1**) which can react in radical chain processes. Directly analogous N-hydroxypyridine-2-thione carbamates (**2**) can be prepared readily by the method outlined in Scheme 1. Yields of recrystallized products were typically 70-90%. A general procedure is given below.

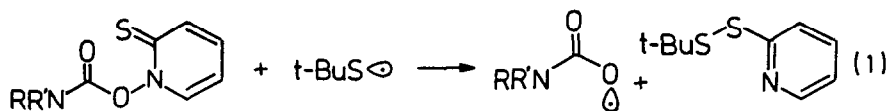


Procedure Reactions were run under nitrogen. Fifteen mL of dry benzene was added to a 100 mL flask containing 1.5 g (0.01 mol) of *N*-hydroxypyridine-2-thione sodium salt (Fluka) and a magnetic stirring bar. The flask was fitted with an addition funnel and sealed with a rubber septum stopper. The flask was placed in an ice bath and stirring was commenced. A solution of phosgene in toluene (5 mL of 20% phosgene) was added via syringe to the addition funnel and then added dropwise to the stirred reaction mixture. The reaction mixture containing solid precipitate was stirred for an additional 45 min at 0 °C after the addition of phosgene was complete and then was stirred for 60 min after warming to 25 °C. A mixture of 0.01 mol of a dialkylamine and 1.0 g of triethylamine was placed in the addition funnel. The reaction flask was wrapped with aluminum foil to shield it from light, and the amine--base mixture was added dropwise to the stirred reaction mixture at 25 °C at a rate such that the temperature of the reaction did not rise. After the addition, the reaction mixture was stirred at 25 °C for 4 h. The reaction mixture was treated with 25 mL of water, the phases were separated, and the organic phase was washed with 25 mL of sat'd aqueous NaCl solution. After drying over MgSO₄, the reaction mixture was filtered, and the solvent was distilled at reduced pressure at 25 °C. Most of the crude products were purified by dissolving the residue in ca. 10 mL of toluene, dilution of this solution with ca. 50 mL of cyclohexane, and crystallization at 0 °C. Alternatively, the products could be purified by chromatography (silica gel, ethyl acetate--hexane) with the chromatography column wrapped in aluminum foil to shield it from light.⁷

For a hindered dialkylamine, the above procedure failed. However, it was possible to obtain **2** by first forming a carbamoyl chloride by dropwise addition of the amine to a phosgene solution as shown in Scheme 2.



Dialkylaminy radicals are formed from carbamates **2** by homolytic cleavage of the O--N bond to give carbamoyloxy radicals which then decarboxylate. Various methods for inducing the O--N cleavage are possible including thermal or photochemical decomposition of **2** or reaction of **2** in AIBN-initiated radical chain reactions employing either tri-*n*-butylstannane or *tert*-butylthiol as the chain carriers as shown in the sequence in Eq 1-3.



Dipropylaminyl radical was produced by decomposition of **2** ($R = R' = C_3H_7$) by various methods, and the ratio of dipropylamine to N-propylidenepropylamine was measured (Table). When no hydrogen atom source was available, the radicals disproportionated. It is noteworthy that unlike the case of simple alkyl radicals generated from ester **1**, the dipropylaminyl radical did not react with **2** via the reaction in Eq 4 to establish a chain reaction.

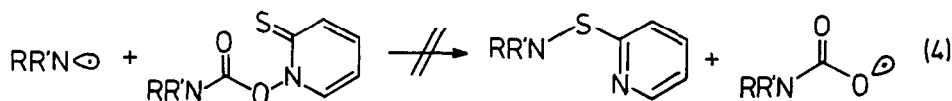


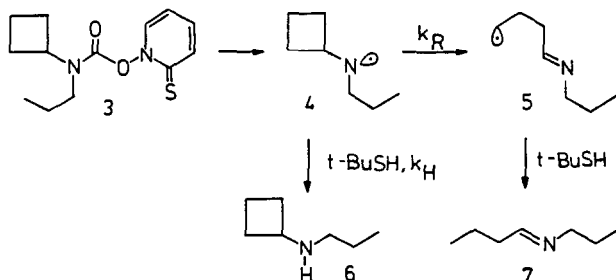
Table. Dipropylamine and N-propylidenepropylamine yields from reactions of carbamate **2** ($R = R' = C_3H_7$) in benzene.

Conditions	Initiator	Hydrogen Donor	% Yield ^a	Ratio ^a
50 °C, 1h ^b	none	none	14	1:1
50 °C, 1h, hv ^c	none	none	70	1:1
50 °C, 6h	AIBN ^d	<i>n</i> -Bu ₃ SnH (1 equiv)	85	16:1
50 °C, 0.5h	AIBN ^d	<i>t</i> -BuSH (1 equiv)	70	>70:1

^a Absolute % yield of amine and imine, ratio of amine to imine. ^b The reaction proceeded only to low conversion of **2** in this experiment. ^c Irradiation with 150 W tungsten lamp. ^d 1-2 mol-% of AIBN was used.

In the presence of hydrogen atom donors the dipropylaminyl radical was primarily reduced. In order to estimate the rate of capture of a dialkylaminyl radical by a hydrogen atom donor, we employed carbamate **3** in the sequence shown in Scheme 3. The ring opening of radical **4** was studied by Ingold and Maeda,⁴ but because of experimental problems, it is possible that the value for the rate constant they found is only a lower limit.^{8,9} Nevertheless, we could determine the relative rates of the first order opening of **4** and of the pseudo-first order trapping of **4** by *t*-BuSH according to the equation: $\%7/\%6 = k_R/k_H * 1/[t\text{-BuSH}]$. At 50 °C, the ratio k_H/k_R was $5 \pm 1 \text{ M}^{-1}$ (13 measurements in three data sets, the error is one standard deviation). Therefore, using Ingold and Maeda's value⁴ for k_R at 50 °C of $5 \times 10^5 \text{ s}^{-1}$ as a minimum for k_R , the minimum rate constant k_H for capture of **4** by *t*-BuSH at 50 °C is $2\text{-}3 \times 10^6 \text{ M}^{-1} \text{ s}^{-1}$ which is comparable to the rate constant for trapping a carbon radical by Bu₃SnH (3.8×10^6 at 50 °C).¹⁰ Two determinations for the minimum rate constant for trapping **4** by Bu₃SnH at 50 °C gave $k_H = 8 \times 10^4 \text{ M}^{-1} \text{ s}^{-1}$.

Scheme 3



Ring openings of cyclopropylaminyl radicals may be important steps in mechanism based enzyme inhibition by cyclopropylamines.¹¹ Ingold and Maeda attempted to measure the rate of one such rearrangement, but reported that the ring opening of aminyl radical **8** to give radical **9** was too fast to measure by their ESR method.⁴ When carbamate **2** (R = butyl, R' = cyclopropyl) was studied by the method in Scheme 3, large concentrations of *t*-BuSH were required to trap **8** before ring opening. The reactions were complicated, but, from the yields of cyclopropylbutylamine, we estimate an approximate k_H/k_R of 0.1 M^{-1} at 50°C . With the reasonable assumption that the rates of aminyl radical trapping by *t*-BuSH are relatively insensitive to sterics,¹⁰ the radical ring opening at 50°C of **8** has a rate constant which is about 50 times greater than that of radical **4**.



We have shown that the readily available carbamates **2** are good sources of dialkylaminyl radicals under controllable conditions. We are continuing to explore both kinetic and synthetic aspects of this methodology.

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References and Notes

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- Carbamates **2** prepared via Scheme 1: R = R' = Pr¹² (mp 80°C); R = *c*-Bu, R' = Pr¹² (mp $48-49^\circ \text{C}$); R = *c*-Pr, R' = Bu¹² (mp $56-60^\circ \text{C}$); R = Bu, R' = 4-pentenyl¹² (mp $79-81^\circ \text{C}$); R = Bu, R' = 5-methyl-4-pentenyl^{12a} (oil). Carbamate **2** in Scheme 2: (mp $88-91^\circ \text{C}$).¹²
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