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Amidyl Radicals from *N*-(Phenylthio)amides¶

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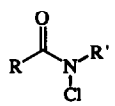
Abstract: Preparations of *N*-(phenylthio)amides from secondary amides are described, and these species are shown to be efficient precursors for amidyl radicals in Bu_3SnH mediated reactions; cyclizations of δ,ε-unsaturated amidyl radicals from these precursors and their use in measurements of relative rate constants are reported.

The utility of radical reactions has increased as new methods for generation of radicals have evolved and as the kinetics of radical reactions have been determined. Most synthetic applications of radicals involve carbon-centered radicals, but reactions of heteroatom-centered radicals also have been studied. Nitrogen-centered radicals include aminyl, aminium cation, iminyl and amidyl radicals.[1,2] The latter, which offer the synthetic advantages of high reactivity and neutral reaction conditions, have been prepared from *N*-chloro- (**1**)[2a] and *N*-nitrosoamides (**2**)[2] and more recently from two members of the PTOC[3] class of radical precursors, PTOC imidate esters (**3**)[4] and *N*-acyl PTOC carbamates (**4**).[5] Here we report that *N*-(phenylthio)amides (**5**) are convenient sources of amidyl radicals in tributyltin hydride mediated reactions. Alkyl chalcogenides are well known sources of carbon-centered radicals in tin hydride mediated reactions, and, recently, arylsulfenamides[6] and *N*-sulfenylimines[7] were found to be useful precursors to aminyl and iminyl radicals, respectively.



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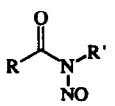

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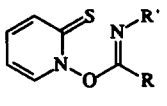

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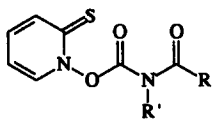

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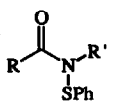
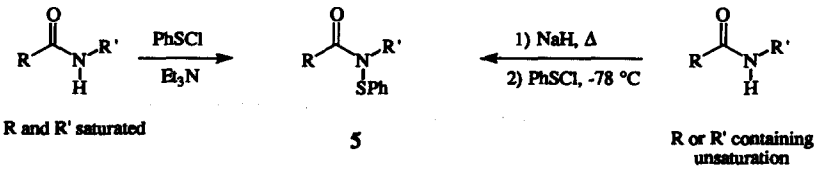


5

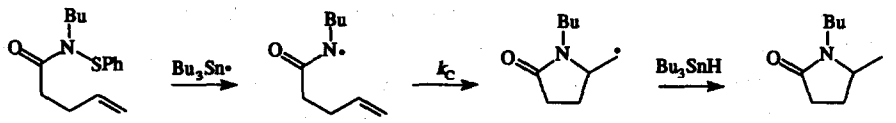
Simple *N*-(phenylthio)amides such as the derivative from *N*-methylacetamide (**5a**; R = R' = CH_3) can be prepared in excellent yield by reaction of a secondary amide with phenylsulfenyl chloride and triethylamine (Method A). For alkenylamides in which electrophilic attack of the double bond by PhSCl was possible, the amide was deprotonated with NaH, and the resulting amide anion was allowed to reaction with PhSCl at -78 °C (Method B). Attempts to employ PhSSPh as the electrophile in Method B were unsuccessful; at the higher reaction temperatures required for electrophilic attack of the amide anion by PhSSPh, α-(phenylthio)amides were produced, apparently from reactions of amide enolates. The *N*-(phenylthio)amides were stable to silica gel chromatography and GC analysis which was employed to determine reagent purities. All compounds **5** were analyzed by ^1H and ^{13}C NMR spectroscopy and HRMS.

¶From the Ph.D. Thesis of JEL, Texas A&M University, 1992; work performed at Wayne State University.

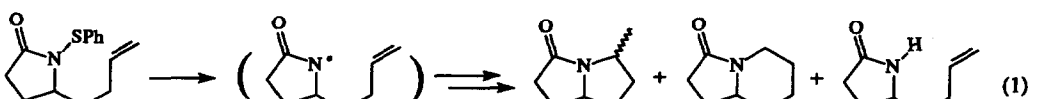


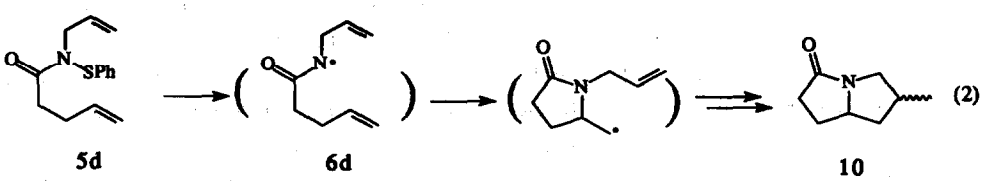
The efficacy of compounds **5** as amidyl radical precursors was tested by generating amidyl radicals that could cyclize in a 5-*exo* fashion. Scheme 1 contains an example. Previously, we had found that the relative rate constants for cyclization and Bu_3SnH trapping of radical **6b** were $k_c/k_H = 0.83$ M at 20 °C;[4b] therefore, a procedure involving low concentrations of tin hydride was required to provide good yields of cyclic product. When precursor **5b** was allowed to react with Bu_3SnH in benzene at 65 °C with addition of tin hydride in aliquots, lactam **7**[8] was formed in 86% yield by GC (77% isolated) (Method C).

Scheme 1



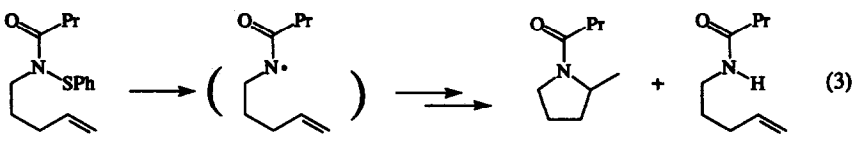
A similar reaction of precursor **5c** gave 8-methyl-2-pyrrolizidinone (**8**),[8] indolizidinone (**9**)[8] and starting amide in 51%, 7% and 5% isolated yields, respectively (eq 1). The formation of the 6-*endo* cyclization product **9** and uncyclized amide from Bu_3SnH trapping shows that the 5-*exo* cyclization of radical **6c** is slower than that of **6b**; we presume that this reflects conformational constraints in radical **6c**. A tandem radical cyclization was achieved with **5d** (eq 2) which gave 7-methyl-2-pyrrolizidinone (**10**)[8] in 95% isolated yield as a 3:1 mixture of diastereomers.





In applications of radical chain reactions in synthesis, relative rate constants for partitioning of a radical intermediate between two reaction channels are necessary for rational planning, but little information concerning the rate constants for reactions of amidyl radicals is available. Therefore, we have employed precursors **5b** and **5e** in competition kinetic studies. Four reactions of **5b** were conducted at 65 °C in benzene in the presence of excess Bu_3SnH at concentrations ranging from 0.17 to 0.87 M, and the relative yields of lactam product **7** and acyclic amide were determined by GC. In the presence of an essentially unchanging concentration of Bu_3SnH, the relative rate constants for cyclization (k_c) and tin hydride trapping (k_H) are given by the equation $(k_c/k_H) = (C/A)\,[Bu_3SnH]^{-1}$ where (C/A) is the ratio of cyclic to acyclic products. For the four reactions of **5b**, a plot of (C/A) against $[Bu_3SnH]^{-1}$ had a slope (i.e. k_c/k_H) of 1.7(1) M.[9]

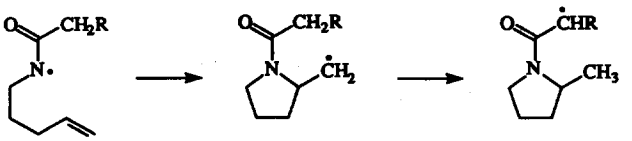
A similar kinetic study was conducted with precursor **5e** which reacted in the presence of varying amounts of tin hydride to give the acylpyrrolidine **11** and acyclic amide. Four reactions were conducted at 65 °C with Bu_3SnH concentrations ranging from 0.06 to 0.37 M. The plot of (C/A) versus $[Bu_3SnH]^{-1}$ had a slope of 0.41(1) M.[9]



(3)

5e **6e** **11**

One may assume that the rate constants for tin hydride trapping of secondary amidyl radicals **6b** and **6e** are approximately equal. Therefore, the 5-*exo* cyclization onto the acyl chain in radical **6b** is about 4 times faster than the corresponding 5-*exo* cyclization onto the alkyl side chain in radical **6e**. This result agrees with product studies which indicated that the two types of 5-*exo* cyclizations occurred with comparable rate constants;[4,5] however, it does not agree with a previous kinetic investigation by Sutcliffe and Ingold[11] who studied the rate constants for cyclization of related amidyl radicals by kinetic ESR spectroscopic methods. Extrapolation of their[10] low temperature results gave rate constants at 27 °C of $>1 \times 10^7$ s^{-1} for 5-*exo* cyclization onto the acyl chain and 5×10^4 s^{-1} for 5-*exo* cyclization onto the alkyl chain. However, the value for the alkyl side chain reaction was a lower limit based on the failure to detect cyclic radical **12** (R = H). Kinetic ESR spectroscopy is limited by the "visibility" of the radicals, and we speculate that the (unobserved) radical **12** (R = H) actually was formed but further reacted, possibly by a 1,5-hydrogen atom transfer, a radical translocation, to give α-amidyl radical **13** (eq 4) that was not detected. Such a radical translocation in **12** (R = Et) from cyclization of **6e** was observed previously when the radical was generated in the absence of efficient radical trapping agents.[4b]



(4)

12 **13**

In summary, *N*-(phenylthio)amides can be prepared in good to excellent yields from secondary amides. In radical-based synthetic applications where reductions of the final product are desired, these precursors are good sources of amidyl radicals via tributyltin hydride mediated reactions.

Experimental Procedures

Method A. To a solution of *N*-methylacetamide (2.5 mmol) and Et_3N (2.8 mmol) in CCl_4 (15 mL) was added PhSCl[11] (2.65 mmol). The mixture was heated in a 45 °C bath for 3 h. After cooling, Et_2O (20 mL) was added to precipitate salts, and the mixture was filtered. The filtrate was washed with 10% $NaHCO_3$ soln, dried over $MgSO_4$, and concentrated under reduced pressure. Column chromatography of the residue (silica gel, hexanes-ethyl acetate elution) gave *N*-methyl-*N*-(phenylthio)acetamide (2.3 mmol, 90%) as a colorless oil.

Method B. To a suspension of NaH (2.8 mmol) in THF was added the amide (2.5 mmol). The mixture was heated at 50 °C until H_2 evolution ceased (ca. 4 h). The mixture was cooled to -78 °C, and PhSCl (2.7 mmol) was added dropwise until the yellow color was persistent for ca. 2 min. Solvent was removed under reduced pressure, and the residue was partitioned between Et_2O (20 mL) and H_2O (10 mL). The organic phase was dried ($MgSO_4$), filtered, and concentrated. Column chromatography (silica gel, hexanes-ethyl acetate elution) gave the desired *N*-(phenylthio)amides (**5**) in 41-74% yields as colorless oils.

Method C. A solution of precursor **5** (1 mmol) in degassed benzene (20 mL) was heated to 65 °C under N_2. A soln containing Bu_3SnH (1.2 mmol) and AIBN (0.05 mmol) in benzene was added in 12 aliquots at 15 min intervals. The resulting soln was analyzed by GC. Products were isolated by column chromatography (silica gel, hexanes-ethyl acetate elution).

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References and Notes

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8. Compounds **7** and **11** are known.[4b] Compounds **8** (one diastereomer) and **9** and compounds **10** (mixture of diastereomers) were obtained as inseparable mixtures; they were characterized by ^1H and ^{13}C NMR spectroscopy and GC-mass spectrometry.
9. The error at 2σ in the last significant figure is given in parentheses.
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