First examples of intramolecular addition of primary amidyl radicals to olefins[1]

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Abstract: The first examples of intramolecular addition of primary amidyl radicals to olefins are described. Amidyl radicals were generated from *N*-(phenylthio)amides in refluxing benzene using a catalytic amount of 2,2′-azobis(isobutyronitrile) (5 mol%) and tributyltin hydride (~2.2 equiv.). The resulting yields of cyclic products ranged from 63% to 85%.

Key words: radical cyclization, amidyl radicals, nitrogen heterocycles.

Résumé : Les premiers exemples de cyclisation radicalaire impliquant un radical amidyle primaire et une oléfine sont décrits. Les radicaux amidyles sont obtenus à partir de *N*-(phénylthio)amides dans le benzène à reflux en présence d'une quantité catalytique de 2,2′-azobis(isobutyronitrile) (5 mol%) et d'hydrure de tributylétain (~2.2 équiv.). Des rendements en produits cyclisés variant de 63 % à 85 % sont obtenus.

Mots clés : cyclisation radicalaire, radicaux amidyles, hétérocycles azotés.

Introduction

Over the years, amidyl radicals have attracted continuous interest with regard to their structure (1, 2), their reactivity (3–5), and ways to generate them (3, 4). Clearly, it appears that intramolecular addition of an amidyl radical on a pendant olefin is a powerful synthetic tool for the formation of nitrogen-containing heterocycles. Numerous examples of cyclization involving secondary amidyl radicals can be found in the literature (4). However, as far as we know, there are no examples of a successful cyclization involving a primary amidyl radical (4*k*, 6), even if there are many examples of successful intermolecular additions of primary amidyl radicals to olefins (3). The main reason for the lack of data on the cyclization of primary amidyl radicals is that endeavours to prepare the usual radical precursors such as *N*-haloamides (3, 4*a*, 4*b*), *N*-(pyridine-2-thione-oxycarbonyl) amides (PTOC amides) (4*c*, 4*f*), and *N*-(ethoxythiocarbonylsulfanyl)amides (4*h*), have failed when applied to olefinic primary amides (7).[3] In the present paper, we report that *N*-(phenylthio) derivatives of olefinic primary amides can be easily prepared and that nitrogen heterocycles resulting from their radical cyclization can be obtained in good to very good yields.

The four olefinic primary amides **5**–**8** were selected as models for radical cyclization of primary amidyl radicals. They were prepared from the corresponding carboxylic acids **1**–**4** via the acid chlorides as shown in Scheme 1.[4] Carboxylic acids **1**, **2**, and **4** are commercially available and cyclohept-4-ene carboxylic acid **3** was synthesized in four steps from cyclopentanone following a method developed by Stork and Landesman (8).

Next, conversion of primary amides **5**–**8** into suitable amidyl radical precursors was examined. We found that *N*-(phenylthio)amides **9**–**12** could be easily prepared in good to very good yields (60%–84%) following a protocol developed by Esker and Newcomb (4*d*), but slightly modified, by reacting the anion of the amide with phenylsulfenyl chloride (9).[4] *N*-(Phenylthio)amides **9**–**12** were the sole amidyl precursors that could be obtained from olefinic primary amides **5**–**8**.[3]

Having the primary amidyl radical precursors in hand, intramolecular addition was next investigated. *N*-

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This paper is dedicated to Howard Alper in recognition of his many achievements in chemistry.

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[3]We tried to prepare *N*-(PTOC)amides (4*c*, 4*f*) and *N*-(ethoxythiocarbonylsulfanyl)amides (4*h*) of primary amides **5**–**7**, but all attempts were unsuccessful.

[4]Supplementary material: general procedures for the preparation of primary amides **5**–**8** and of *N*-(phenylthio)amides **9**–**12**; spectroscopic data of compounds synthesized. Supplementary data for this article are available on the Web site or may be purchased from the Depository of Unpublished Data, Document Delivery, CISTI, National Research Council Canada, Ottawa, ON K1A 0S2, Canada. DUD 3661. For more information on obtaining material refer to http://cisti-icist.nrc-cnrc.gc.ca/irm/unpub_e.shtml.

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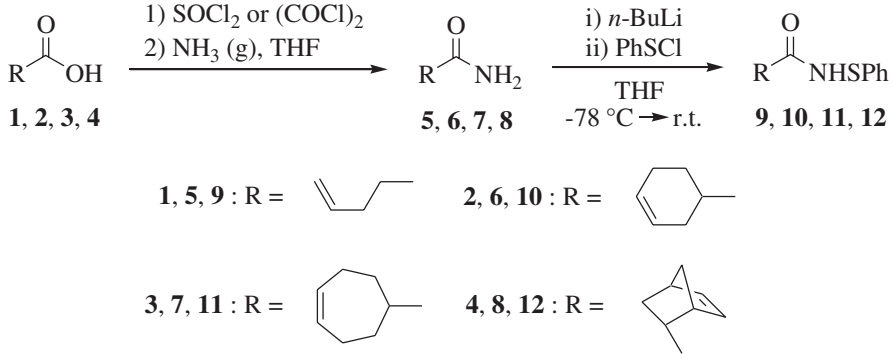
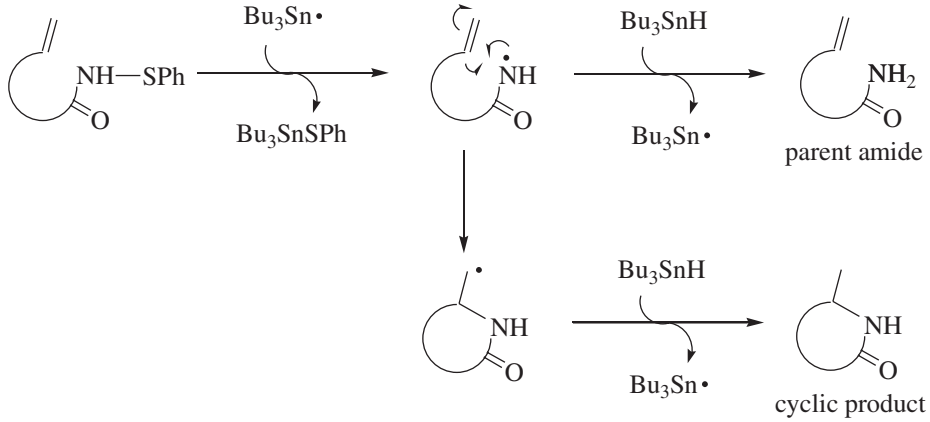
Scheme 1. Preparation of primary amides and *N*-(phenylthio) derivatives.



Scheme 2. Radical chain mechanism.

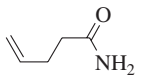
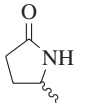
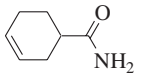
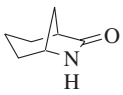
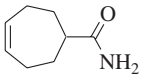
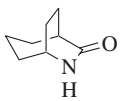
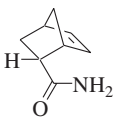
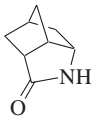


(Phenylthio)amides **9**–**12** were heated in refluxing benzene and a solution of 2,2′-azobis(isobutyronitrile) (AIBN) (5 mol%) and tributyltin hydride (~2.2 equiv.) in benzene was added. As shown in Table 1, all four models underwent radical cyclization to afford the corresponding heterocyles **13**–**16**[4] in good to very good yields (63%–85%). Interestingly, the use of less than ~2.2 equiv. of tributyltin hydride resulted in incomplete conversion of the starting olefinic *N*-(phenylthio) amide.

As expected (10), 5-*exo*-trig cyclizations were favoured over 6-*endo*-trig cyclizations for all concerned models (entries 1, 2, and 4). Also, 6-*exo*-trig cyclization occurred in good yield (71%) when this was the sole possibility (entry 3). The reactions also gave small amounts of the parent amide (8%–16% yield) as a result of the reduction of the amidyl radical by tributyltin hydride. The radical chain mechanism involved is illustrated in Scheme 2.

To the best of our knowledge, this paper reports the first examples of radical cyclizations involving a primary amidyl radical and a pendant olefin. Olefinic *N*-(phenylthio)amides were prepared in good yields (60%–84%) and used as primary amidyl radical precursors in a reaction with AIBN in catalytic amount (5 mol%) and tributyltin hydride (~2.2 equiv.), acting, respectively, as radical initiator and chain carrier. Good to very good yields of cyclization were obtained (63%–85%). Thus, it is no longer necessary to prepare an N-protected precursor and then remove the protecting group after cyclization (4*k*). Further studies are currently being conducted.

Table 1. Cyclization results.

Entry	Primary amide	*N*-(PhS)amide[a]	Cyclic product[b,c]
1	 **5**	**9** 84%	 84% **13**
2	 **6**	**10** 63%	 85% **14**
3	 **7**	**11** 64%	 71% **15**
4	 **8**	**12** 60%	 63% **16**

[a]Reaction conditions: (*i*) *n*-BuLi, (*ii*) PhSCl, THF, –78 °C → r.t.
[b]Reaction conditions: $AIBN_{cat}$–Bu_3SnH (slow addition), benzene, reflux.
[c]Yield of parent amide: 8%, 11%, 16%, and 16% in entries 1–4, respectively.

General procedure for cyclization

To a refluxing solution of *N*-(phenylthio)amide (0.5 mmol) in anhydrous and degassed benzene (20 mL) under a nitrogen atmosphere, 2,2′-azobis(isobutyronitrile) (4 mg, 0.024 mmol) and tributyltin hydride (0.28 mL, 1.0 mmol) dissolved in anhydrous and degassed benzene (10 mL) were added over 4 h. If required, a small additional amount of AIBN–Bu_3SnH in benzene was added to complete the reaction. The solvent was removed under reduced pressure and the residue was purified by flash chromatography (acetone–toluene, 2:3) monitored by GC to afford the desired lactam.

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