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A New Tin-Free Source of Amidyl Radicals

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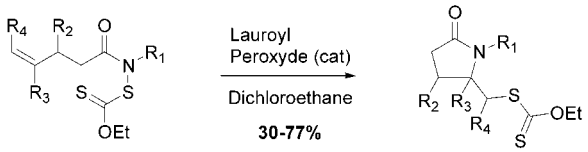
ABSTRACT

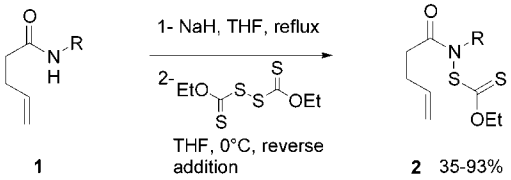


The readily available *N*-(*O*-ethyl thiocarbonylsulfanyl)amides are powerful amidyl radical precursors that undergo 5-*exo* cyclization to give pyrrolidinone derivatives via a radical-chain reaction initiated by a small amount of lauroyl peroxide.

Amidyl radicals have been recognized over the past few years as useful intermediates for the construction of nitrogen-containing heterocycles.[1] Thus, intramolecular cyclization of an amidyl radical onto an olefin allows the construction of functionalized pyrrolidinones,[2] which can be further elaborated into more complex structures such as alkaloids.[3] However, most of the reported methods are based on stannane technology leading to well-known difficulties of purification and toxicity. As part of our continuing effort in this area,[4] we wondered if the process based on the addition−fragmentation to dithiocarbonyl derivatives we extensively developed for the generation of carbon-centered radicals[5] could be applied to amidyl radicals.

For this study, an easy access to *N*-(*O*-ethyl thiocarbonylsulfanyl)amides **2** was needed. These hitherto unreported compounds were eventually readily obtained by a modification of a procedure developed by Newcomb and co-workers for the synthesis of *N*-phenylthioamides.[2e] Thus, deprotonation of amide **1** with sodium hydride in refluxing THF following by inverse addition of the amide salt into a solution of bis-ethoxythiocarbonyldisulfane in excess furnished the desired radical precursor **2** as a reasonably stable yellow oil in yields ranging from 35 to 93% (Scheme 1 and Table 1).

Scheme 1



We were pleased to find that when a solution of **2a** in refluxing 1,2-dichloroethane was treated with a small amount of lauroyl peroxide (DLP), a 63% yield of the desired cyclized product **3a** was obtained. The cyclization proceeds

(1) For recent reviews of the chemistry of nitrogen centered radicals, see: (a) Fallis, A. G.; Brinza, I. M. *Tetrahedron* **1997**, *53*, 17543. (b) Zard, S. Z. *Synlett* **1996**, 1148−1155. (c) Esker, J. L.; Newcomb, M. *Adv. Heterocycl. Chem.* **1993**, *58*, 1. For a recent review on the synthesis of heterocycles by radical cyclisation, see: Bowman, W. R.; Bridge, C. F.; Brookes, P. *J. Chem. Soc., Perkin Trans. 1* **2000**, *1*, 1.

(2) For notable examples of amidyl radicals generation and cyclization, see: (a) Lin, X.; Stien, D.; Weinreb, S. M. *Tetrahedron Lett.* **2000**, *41*, 2333. (b) Clark, A. J.; Filik, R. P.; Peacock, J. L.; Thomas, G. H. *Synlett* **1999**, *4*, 441. (c) Clark, A. J.; Deeth, R. J.; Samuel, C. J.; Wongtap, H. *Synlett* **1999**, *4*, 444. (d) Esker, J. L.; Newcomb, M. *J. Org. Chem.* **1994**, *59*, 2779. (e) Esker, J. L.; Newcomb, M. *Tetrahedron Lett.* **1993**, *34*, 6877. (f) Esker, J. L.; Newcomb, M. *J. Org. Chem.* **1993**, *58*, 4933.

(3) We recently completed a short synthesis of (±)-γ-lycorane involving a cascade process starting with a nitrogen-centered radical: Hoang-Cong, X.; Quiclet-Sire, B.; Zard, S. Z. *Tetrahedron Lett.* **1999**, *39*, 2125.

(4) (a) Callier-Dublanchet, A.-C.; Quiclet-Sire, B.; Zard, S. Z. *Tetrahedron Lett.* **1995**, *36*, 8791. (b) Boivin, J.; Callier-Dublanchet, A.-C.; Quiclet-Sire, B.; Zard, S. Z. *Tetrahedron* **1995**, *51*, 6517. (c) Callier, A.-C.; Quiclet-Sire, B.; Zard, S. Z. *Tetrahedron Lett.* **1994**, *35*, 6109.

(5) For reviews of our work on xanthates, see: (a) Quiclet-Sire, B.; Zard, S. Z. *Phosphorus, Sulfur, Silicon* **1999**, 137. (b) Zard, S. Z. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 672.

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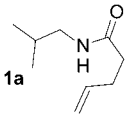
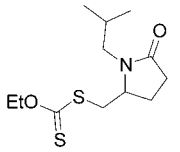
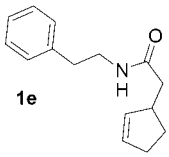
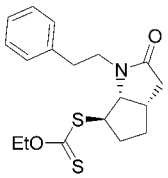
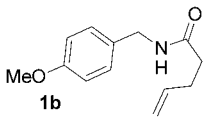
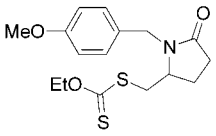
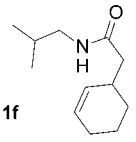
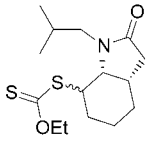
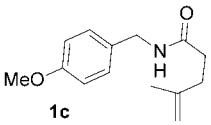
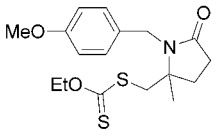
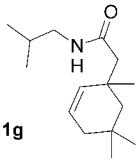
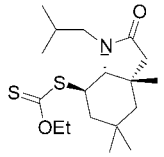
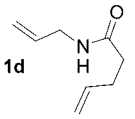
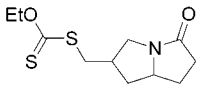
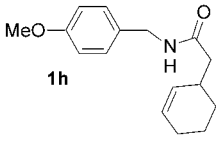
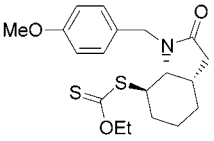
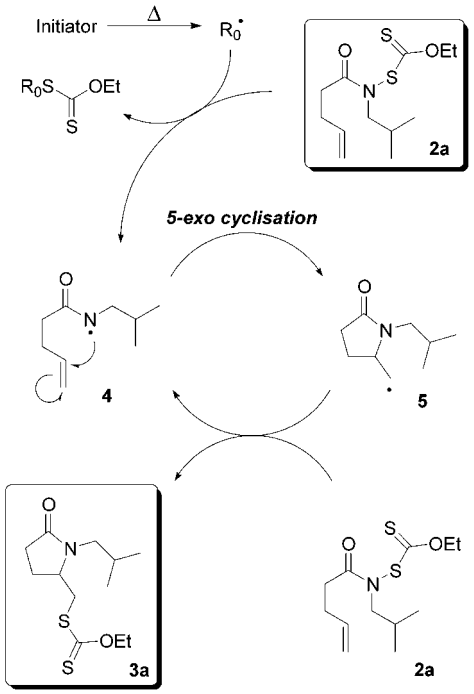
Table 1. Formation of *N*-(*O*-Ethyl thiocarbonylsulfanyl)amides **2** and Radical Cyclization Leading to **3**

amide **1**	yield of xanthate **2**	product **3**	yield of **3**	amide **1**	yield of xanthate **2**	product **3**	yield of **3**
 **1a**	**2a** 35%		**3a** 63%	 **1e**	**2e** 65%		**3e** 70%
 **1b**	**2b** 76%		**3b** 62%	 **1f**	**2f** 69%		**3f** 77% (8/2)
 **1c**	**2c** 93%		**3c** 30%	 **1g**	**2g** 48%		**3g** 72%
 **1d**	**2d** 84%		**3d** 47% [a] 63% [b]	 **1h**	**2h** 68%		**3h** 72%[c]

[a] In 1,2-dichloroethane with 13 mol % of lauroyl peroxide. [b] In chlorobenzene with 7.5 mol % of cumyl peroxide. [c] Tetracyclic compound **6** was also isolated in 15% yield.

as shown in Scheme 2. Radical $R_0^{\bullet}$, produced by thermal decomposition of the initiator, exchanges a xanthate group with substrate **2a** to give the desired amidyl radical **4**, which undergoes a 5-*exo* addition to the internal olefin. The resulting cyclized radical **5** finally adds to the thiocarbonyl of the starting xanthate **2a**, thus producing the pyrrolidinone **3a** and regenerating the amidyl species **4** to propagate the chain.

Scheme 2. Chain Radical Cyclization of Amidyl Radical **2a**



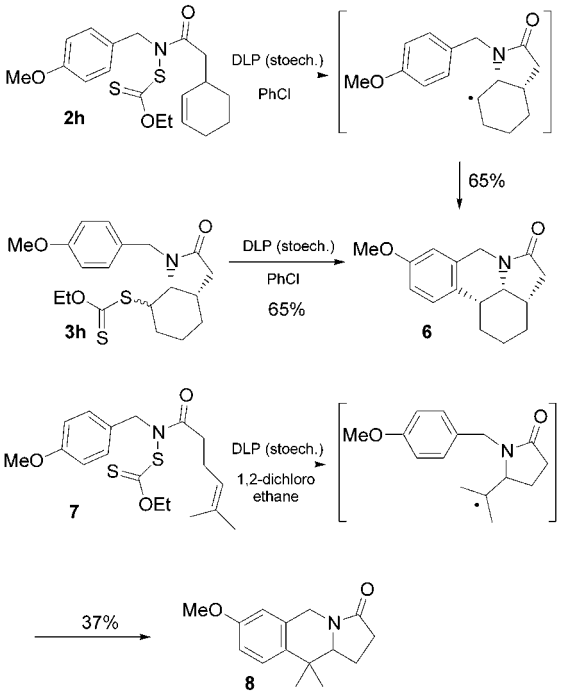
N-(*O*-Ethyl thiocarbonylsulfanyl)amides turned out to be quite effective radical precursors for the construction of monocyclic (**3a**−**c**) and bicyclic (**3d**−**h**) pyrrolidinones, as demonstrated by the examples in Table 1.

In the case of xanthate **2c**, the cyclization occurred by a 5-*exo* mode to give **3c** containing a quaternary center. None of the isomer corresponding to the 6-*endo* mode of cyclization could be isolated, but the cause for the modest yield in this case remains unclear.

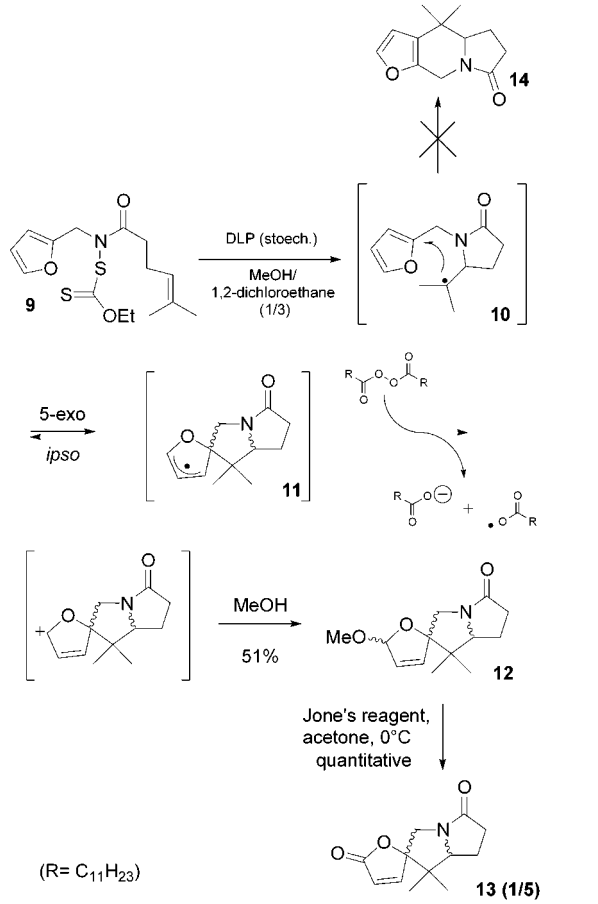
More complex molecules may be constructed by further transformation of the cyclized product or by implementing another radical sequence (Scheme 3). In the case of **3h**, refluxing in chlorobenzene with a gradual addition of a stoichiometric amount of lauroyl peroxide induced ring closure onto the aromatic ring to give the somewhat unstable tetracyclic product **6** in 65% yield. This compound, which possesses the galanthane skeleton of the Amaryllidaceae alkaloids, may be directly obtained under the same conditions from **2h** in 65% yield.[6] In a similar way, radical precursor **7**

(6) It is interesting to note that a similar cyclization using stannane-based methodology,[3] which was successful with a substituted benzoyl group on the nitrogen, failed with the *N*-benzyl analogue (Hoang Cong, X.; Zard, S. Z. Unpublished results).

Scheme 3. Radical Cascade Cyclization of Precursor **2h** and **7**



Scheme 4. Radical Cascade Cyclization of Precursor **9**



furnished indolizidinone **8** in 37% yield by treatment with lauroyl peroxide in refluxing 1,2-dichloroethane.

We also found fortuitously that the radical cascade could be combined with an oxidation process. Thus, when radical precursor **9** was submitted to the same conditions for a radical cascade cyclization (gradual addition of a stoichiometric amount of lauroyl peroxide in a 1/3 refluxing mixture of methanol/1,2-dichloroethane), the unexpected spiro pyrrolizidinone **12** was isolated as a complex mixture of isomers (Scheme 4).

Because of its instability, compound **12** was subsequently treated with Jones reagent in acetone at 0 °C[7] to furnish the tricyclic spiro furanone **13** in quantitative yield as a 1/5 mixture of isomers. The formation of pyrrolizidinone **12** may be rationalized by an *ipso* addition of the cyclized radical **10** onto the furan ring. The resulting delocalized radical is apparently sufficiently electron-rich to undergo electron transfer to the lauroyl peroxide, thus furnishing a carbocation that is finally quenched by methanol. It has to be noted that this cascade, causing dearomatization of the furan ring, is in sharp contrast with the one involving radical precursor **7** since the corresponding compound **14** is not formed under these conditions. It is possible that in the case of **7** the *ipso* cyclization is more easily reversible and also that the radical from this mode of cyclization is not as cleanly oxidized. The latter possibility may explain the modest yield of **8**.[8]

In conclusion, these preliminary results demonstrate the potential of this mild approach for generating amidyl radicals and for allowing the expedient synthesis of a variety of highly functionalized five-membered nitrogen containing heterocycles.

Acknowledgment. We wish to thank Rhodia Chimie Fine for generous financial support and Drs Jean-Marc Paris and François Metz of Rhodia for friendly discussions.

Supporting Information Available: Detailed experimental procedures and spectra data for compounds **1a**−**h**, **2a**−**h**, **3a**−**h**, **6**, **7**, **8**, **9**, and **13**. This material is available free of charge via the Internet at http://pubs.acs.org.

OL026221M

(7) Machado-Araujo, F. W.; Gore, J. *Tetrahedron* **1982**, *38*, 2897.

(8) For another example of ipso radical cyclization and loss of aromaticity, see: Boivin, J.; Yousfi, M.; Zard, S. Z. *Tetrahedron Lett.* **1997**, *38*, 5985.