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Intramolecular Cyclization of Acyl Radicals onto the Azido Group: A New Radical Approach to Cyclized Lactams[†]

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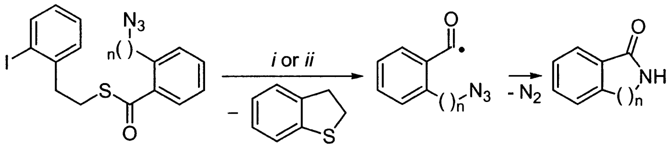
ABSTRACT



Reagents: *i*, Bu$_3$SnH/AIBN; *ii*, (TMS)$_3$SiH/AIBN.

Aryl- and alkyl-derived azidoacyl radicals, generated from thiolesters by intramolecular homolytic substitution at the sulfur, can undergo five- and six-membered cyclization onto the azido moiety to give cyclized lactams.

Radical cyclization reactions have become a powerful tool for the construction of carbocyclic and heterocyclic systems, even those occurring in natural products.[1] Radical cyclizations most often involve carbon−carbon bond formation, whereas those leading to carbon−nitrogen bond formation are much less well documented. The reported methodologies rely on additions of aminyl[2] and iminyl[3] radicals to C═C and C═O double bonds or on additions of carbon radicals to nitrogen atoms of imines.[4] However, the synthetic potential of radical azide reactions has been so far rather poorly investigated, though the reported studies have revealed that the azido moiety can act as a valuable radical acceptor toward carbon- and heteroatom-centered species to yield an aminyl radical after loss of molecular nitrogen by the initial triazenyl adduct.[2e,f,5] In fact, intramolecular additions of aryl,[6] thiocarbonyl,[7] alkyl,[8] and vinyl[9] radicals have been recently found to provide useful synthetic routes to *N*-heterocycles.

[†] Dedicated to Professor Domenico Spinelli on the occasion of his 70th birthday.

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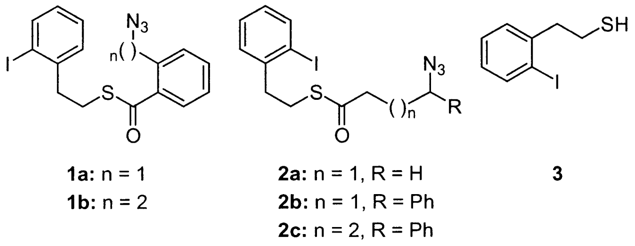
Our long interest in the chemistry of azido and radical species[2e,f,6,7,9,10] prompted us to undertake a study of the chemical behavior of acyl radicals containing an azido moiety in the side chain as a possible radical entry to cyclized lactam systems. Radical reactions of acyl radicals with azides have hitherto been totally unexplored, though the chemistry of acyl radicals has been extensively investigated and shown to exhibit considerable utility in organic synthesis in terms of both intra- and intermolecular carbon−carbon bond-forming reactions.[11] To the best of our knowledge, the only available instances of carbon−nitrogen bond formation with acyl radicals are offered by the intramolecular addition of those radical species onto N−C double bonds affording cyclized 2-pyrrolidinone products.[4d]

In this paper, we report our preliminary results obtained with a number of aryl- and alkyl-derived azidoacyl radicals, which were generated from the thiolester precursors **1a**,**b** and **2a**−**c** (Figure 1) by intramolecular homolytic substitution at sulfur, following a recent methodology reported by Crich and co-workers.[12] The thiolesters **1a**,**b** and **2a**−**c** were generally prepared in high yield by reacting the (iodophenyl)-ethanethiol **3**[12] with the appropriate azidoacyl chlorides. These were in turn readily obtained, by known methodology,[13] from corresponding bromoesters, commercially available or prepared according to the literature.



1a: n = 1
1b: n = 2

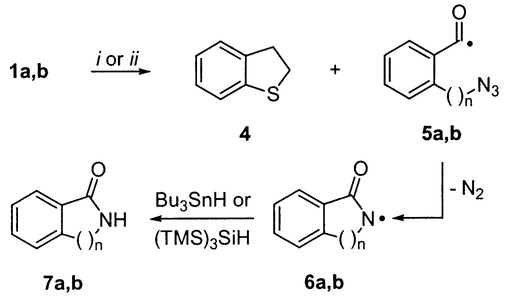
2a: n = 1, R = H
2b: n = 1, R = Ph
2c: n = 2, R = Ph

3

Figure 1.

Radical reactions of the thiolesters **1a**,**b** and **2a**−**c** with the most commonly used reagents, i.e., tri-*n*-butylstannane, tris(trimethylsilyl)silane [$(TMS)_3SiH$], and allyltributyl(or triphenyl)stannane were conducted in benzene solution with AIBN initiation. In light of previous findings of Kim et al.[8] and Murphy et al.,[14] initial tributylstannyl and tris(trimethylsilyl)silyl radicals were actually expected to perform selective iodine abstraction in the presence of the azido moiety, thence allowing release of an azidoacyl radical by the ensuing aryl radical.

Scheme 1[a]



[a] Reagents: (i) Bu_3SnH/AIBN; (ii) $(TMS)_3SiH$/AIBN.

Treatment of the compound **1a** (2 mmol) with Bu_3SnH (2.2 mmol) and AIBN (0.2 mmol) in degassed refluxing benzene (80 mL) for 2 h led to complete consumption of the substrate and formation of the cyclized indolinone **7a**,[15] which, after chromatographic separation of the crude mixture, could be isolated in 87% yield along with the anticipated dihydrobenzothiophene **4** (80%).[12] This finding therefore suggests that the produced acyl radical **5a** was fairly capable of performing intramolecular five-membered cyclization onto the azido moiety yielding the cyclized amidyl radical **6a**, which was eventually reduced by the tin hydride (Scheme 1 and Table 1). Strictly comparable results were obtained when the same radical reaction was performed by using $(TMS)_3SiH$ in place of Bu_3SnH.

Table 1. Radical Reactions of Thiolesters **1a**,**b**

		products (%)	
reagents		**7**	**8**
1a	Bu_3SnH	87	
1a	$(TMS)_3SiH$	81	
1a	$AllylSnBu_3$	45	40
1a	$AllylSnBu_3$	25	60
1b	Bu_3SnH	87	
1b	$(TMS)_3SiH$	75	

Moreover, the reaction of the thiolester **1a** (2 mmol) with excess allyltributylstannane (8 mmol) and AIBN (0.8 mmol) allowed isolation of the allylated indolinone **8** (Figure 2) in 40% yield together with the related compound **7a** to a comparable extent (45%). The observed production of isoindolinone **7a** evidently suggests that the cyclized amidyl radical **6a** could undergo effective H-transfer, e.g., from the reagent stannane, in competition with the expected allyl transfer.[2e,12] Interestingly, when allyltributylstannane was replaced with the corresponding triphenyl derivative, the occurrence of **7a** (25%) could be considerably suppressed in favor of the allylated compound **8** (60%). This fact is consistent with our previous evidence that allyltriphenyl-

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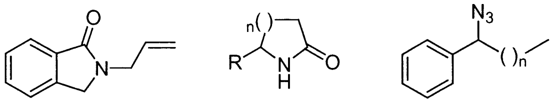
(15) Structural assignment to all the known compounds was performed on the basis of physical and/or spectral data.



8

9a: n = 1, R = H
9b: n = 1, R = Ph
9c: n = 2, R = Ph

10a: n = 1
10b: n = 2

Figure 2.

stannane is superior to the tributyl derivative as a radical allyl-transfer reagent.[2e]

The corresponding reactions of the thiol ester **1b** with Bu_3SnH and $(TMS)_3SiH$ gave the quinolone **7b**[15] in 87 and 75% isolated yield respectively, thus indicating that, in these cases, the derived acyl radical **5b** could smoothly undergo intramolecular six-membered cyclization onto the adjacent azido substituent (Scheme 1 and Table 1).

In contrast with the above aryl-derived azidoacyl radicals, the alkyl-derived ones, which were presently produced from the thiolesters **2a**−**c**, showed a lesser propensity to perform intramolecular addition onto the azido moiety, probably due to their enhanced tendency to undergo decarbonylation reaction. The rate of decarbonylation of alkyl-derived acyl radicals is in fact known to be considerably higher than that of the aryl-derived ones.[11] Upon usual radical reaction with Bu_3SnH/AIBN, the thiolester **2a** gave, besides the dihydrobenzothiophene **4** (83%), the 2-pyrrolidinone **9a**[15] in 35% isolated yield. The corresponding Bu_3SnH reaction of the phenyl-substituted derivative **2b** similarly led to the isolation of the phenylated pyrrolidinone **9b**[15] in modest yield (35%), but in this case, the decarbonylated propyl azide **10a** could be also isolated in 16% yield. Moreover, the phenyl-substituted thiolester **2c** reacted with stannyl radical under standard conditions yielding the pyridinone **9c**[15] in 31% yield, along with a lesser amount of the decarbonylated butyl azide **10b** (15%) (Figure 2 and Table 2).

Table 2. Radical Reactions of Thiolesters **2a**−**c**

reagents		products (%)	
		9	**10**
2a	Bu_3SnH	35	
2b	Bu_3SnH	35	16
2c	Bu_3SnH	31	15

In summary, in the present work we have succeeded in producing acyl radicals bearing an azido group in the side chain for the first time. Under our reaction conditions, the produced azidoacyl radicals were found to behave in a fashion strongly dependent upon their structural features. Indeed, the aryl-derived acyl radicals were highly prone to perform an unprecedented intramolecular five- and six-membered cyclization onto the azido moiety, whereas the alkyl-derived ones were somewhat discouraged due to their peculiar propensity for undergoing concomitant decarbonylation. Further studies are clearly required in order to disclose the full synthetic potential of the cyclization reactions of acyl radicals with azides; nevertheless, at this stage, our findings provide further useful chemical information about the versatile radical reactivity of both acyl radicals and azides.

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Supporting Information Available: General procedures for the preparation of the thiolesters **1a**,**b** and **2a**−**c** and their radical reactions with Bu_3SnH, $(TMS)_3SiH$, allyl$SnBu_3$, and allyl$SnPh_3$, as well as spectral data for all the new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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