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Cyclizations of *N*-Stannylaminyl Radicals onto Nitriles

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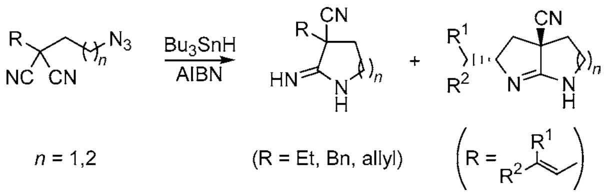
ABSTRACT



Stannylaminyl radicals derived from radical reactions of Bu_3SnH with azidoalkylmalononitriles exhibit highly efficient 5- and 6-exo cyclization onto either nitrile group to give aminoiminyl radicals that in turn are reduced to amidines or undergo successive 5-exo cyclization onto an internal alkene.

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 bonds are much less documented. The reported methods rely on additions of aminyl[1e,2] and iminyl[1e,3] radicals to C═C and C═O double bonds or additions of carbon radicals to nitrogen atoms of imines.[1e,4] The synthetic potential of azide radical reactions has so far been 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] Indeed, intramolecular additions of aryl,[6] thiocarbonyl,[7] alkyl,[8] vinyl,[9]

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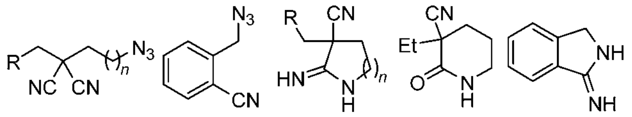
and acyl[10] radicals have provided useful synthetic routes to N-heterocycles.

Moreover, intermolecular addition of stannyl radicals to azides smoothly yields *N*-stannylaminyl radicals that act as the key intermediates in several important synthetic processes. In particular, these nitrogen intermediates, being somewhat more nucleophilic than ordinary aminyl radicals,[11] have been shown to perform three-,[2e,f] five-,[2a] and six-membered[2a] cyclizations onto the carbonyl groups of cyclic ketones and β-keto esters to give ring-expanded amides by β-fragmentation of resulting alkoxyl radicals.

Our long interest in the chemistry of azido and radical species[2e,f,6,7,9,12] prompted us to undertake a study of the intramolecular reactivity of *N*-stannylaminyl radicals toward a cyano group as a possible further entry to carbon−nitrogen bond formation. In sharp contrast with various reports of successful (and also unsuccessful) cyclizations of carbon-centered radicals onto nitriles,[1e,13] those involving aminyl radicals remain to date virtually unknown. The sole example appears to be that recently discovered by Kim and co-workers in the course of their investigation of 1,5-hydrogen transfers from carbon to stannylaminyl radicals.[11] These authors found that the radical reaction of 5-azidovaleronitrile with Bu_3SnD/AIBN afforded a modest yield (27%) of a pyridinimine seemingly arising from 6-exo cyclization of the initial stannylaminyl radical to the nitrile group. This finding is of interest especially in view of the fact that carbon radical cyclization onto nitriles normally occurs in a 5-exo fashion.[1e,13]

In this paper, we report our initial results of the radical reactions of Bu_3SnH with azidonitriles, showing that the derived stannylaminyl radicals are actually highly capable of performing cyclization onto the cyano moiety, giving aminoiminyl radicals that can be reduced to amidines or undergo efficient cyclization onto a suitable alkenyl group.

We first examined the radical reactions of azidomalononitriles **1a**−**c** and azidobenzonitrile **2** (Figure 1). These new azides were generally prepared by treatment of the corresponding bromides with sodium azide. The requisite bromomalononitriles were in turn available from malononitrile[14] through successive alkylations with ethyl or benzyl bromide and then with 1,2-dibromoethane or 1,3-dibromopropane. The known *o*-cyanobenzyl bromide was instead directly obtained by bromination of *o*-tolunitrile.[15]



1a: *n* = 1, R = Me
1b: *n* = 1, R = Ph
1c: *n* = 2, R = Me

2

3a: *n* = 1, R = Me
3b: *n* = 1, R = Ph
3c: *n* = 2, R = Me

4

5

Figure 1.

The reactions of azides **1a**−**c** and **2** were performed by adding a benzene solution of Bu_3SnH (1.1 equiv) and AIBN (0.1 equiv) with a syringe pump over 3 h to a refluxing benzene solution of the appropriate substrate (0.05 M) under a nitrogen atmosphere. The resulting mixtures were refluxed for an additional 2−3 h until virtual disappearance of the starting material and then subjected to column chromatography. In all cases, complex mixtures were formed and problems were encountered in product separation from tin residues.

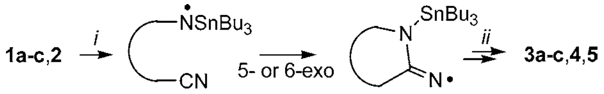
Azides **1a**,**b** and **2** led to isolation of the cyclized amidines **3a**,**b** and **5** in varying yields (30−66%, Figure 1 and Table 1, entries 1−3), whereas azide **1c** gave only a poor yield (15%) of the pyridinone **4**, which was evidently the hydrolytic product of pyridinimine **3c** (Figure 1 and Table 1, entry 4). The structures of all new compounds **3a**,**b**, **4**, and **5** were supported by analytical and spectral data.[16] Our present results with azides **1a**,**b** and **2** appear to provide the first chemical evidence of intramolecular 5-exo ring closure of stannylaminyl radicals to nitriles; the process affords cyclized aminoiminyl radicals and then amidines upon subsequent reduction (Scheme 1). Moreover, the reaction of azide **1c** seemed to substantiate Kim's original evidence[11] that a stannylaminyl radical would be also entitled to add to

Table 1. Cyclization Reactions of Azidomalononitriles **1a**−**c**, **6a**−**d**, and **7a**−**c** and Azidobenzonitrile **2** with Bu_3SnH/AIBN

entry	azide	product (%)[a]	entry	azide	product (%)[a]
1	**1a**	**3a** (30)	8	**6d**	**10d** (80)
2	**1b**	**3b** (55)	9	**7a**	**11a** (65)
3	**1c**	**4** (15)	10	**7b**	**11b** (88)
4	**2**	**5** (66)	11	**7c**	**11c** (88)
5	**6a**	**9a** (60)	12	**8**	**16** (77)
6	**6b**	**10b** (45)	13	**6c**[b]	**9c** (50)
7	**6c**	**10c** (83)	14	**6d**[b]	**9d** (10)

[a] Yields isolated by column chromatography. [b] Reaction carried out in the absence of AIBN.

Scheme 1[a]



[a] Reagents: (i) Bu_3SnH/AIBN; (ii) Bu_3SnH, H_2O.

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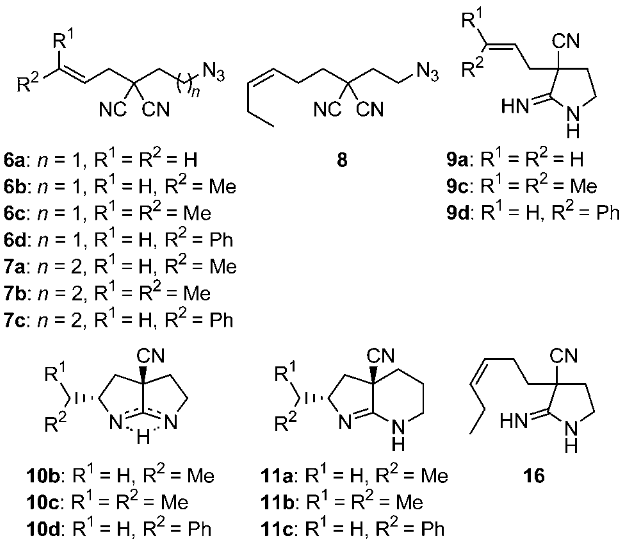
a nitrile in a 6-exo fashion, though possibly to a lesser extent (Scheme 1).

However, at that stage we realized that the actual meaning of the above azide reactions remained rather unclear, since in principle the produced amidines **3a**−**c** and **5** might alternatively have formed through reduction of the stannylaminyl radical by the hydride followed by nucleophilic cyclization of the resulting amine onto the nitrile.[17] Additionally, since stannylaminyl radicals had been found to undergo smooth 1,5-H transfer from carbon to nitrogen when bearing a stabilizing substituent, including a phenyl group, in the 5-position,[11] the benzylated amidine **3b** might also have formed via 1,5-H transfer from the benzylic carbon to the aminyl nitrogen and subsequent cyclization of the reduced aminodinitrile.

To clarify the reactivity of aminyl radical cylization onto nitriles as well as their utility in heterocyclic synthesis, we were subsequently prompted to extend our study to analogous reactions of a number of azidoethyl- and azidopropylmalononitriles, **6a**−**d**,**7a**−**c**, and **8**, each bearing a variously substituted alkenyl moiety as shown in Figure 2. Our aim was to ascertain whether aminoiminyl radicals, possibly generated by 5- and 6-exo stannylaminyl radical cyclization onto either nitrile group, might be intercepted by the internal alkene in 5-exo- (or 6-exo) mode. Very recent reports by Bowman and co-workers have revealed that iminyl radicals generated by 5-exo cyclization of C-centered radicals onto nitriles can undergo tandem cyclizations onto suitably placed alkenes.[13]



6a: $n = 1$, $R^1 = R^2 = H$
6b: $n = 1$, $R^1 = H$, $R^2 = Me$
6c: $n = 1$, $R^1 = R^2 = Me$
6d: $n = 1$, $R^1 = H$, $R^2 = Ph$
7a: $n = 2$, $R^1 = H$, $R^2 = Me$
7b: $n = 2$, $R^1 = R^2 = Me$
7c: $n = 2$, $R^1 = H$, $R^2 = Ph$

8

9a: $R^1 = R^2 = H$
9c: $R^1 = R^2 = Me$
9d: $R^1 = H$, $R^2 = Ph$

10b: $R^1 = H$, $R^2 = Me$
10c: $R^1 = R^2 = Me$
10d: $R^1 = H$, $R^2 = Ph$

11a: $R^1 = H$, $R^2 = Me$
11b: $R^1 = R^2 = Me$
11c: $R^1 = H$, $R^2 = Ph$

16

Figure 2.

The new azido precursors **6a**−**d**, **7a**−**c**, and **8** were generally produced from malononitrile by a methodology similar to that employed for azides **1a**−**c**. The usual reaction of Bu$_3$SnH/AIBN with the allylated azidoethylmalononitrile **6a** yielded the pyrrolidinimine **9a**[16] as the only identifiable product (Figure 2 and Table 1, entry 5). However, the congeners **6b**−**d** interestingly furnished tandem cyclization products, the fused pyrroles **10b**−**d**, respectively, in moderate to good yields (Figure 2 and Table 1, entries 6−8). Similarly, the azidopropylmalononitriles **7a**−**c** also gave the respective tandem cyclization products, the pyrrolopyridines **11a**−**c**, even in somewhat higher yields (Figure 2 and Table 1, entries 9−11). The azidoethylmalononitrile **8**, instead, gave no traces of any tandem product but, like azide **6a**, only led to the monocyclic pyrrolidinimine **16**[16] in fairly high yield (Figure 2 and Table 1, entry 12). No problems of separation from tin residues were encountered in the reactions of azides **6a**−**d**, **7a**−**c**, and **8**.

Since alkyl azides also react with Bu$_3$SnH under thermal conditions, the reactions of azides **6c**,**d** with the tin hydride were repeated in the absence of the radical initiator in order to fully exclude the possibility that our tandem cyclization products might have arisen from some curious nonradical mechanism. In the absence of AIBN, however, the corresponding pyrrolidinimines **9c** and **9d**[16] were obtained as the only identifiable products (Figure 2 and Table 1, entries 13 and 14). Under these circumstances, compounds **9c**,**d** conceivably arose from intramolecular addition of the reduced amine to either cyano group.[17]

As far as the newly observed fused pyrroles **10b**−**d** and pyridines **11a**−**c** are concerned, their structures were primarily suggested by analytical and ^{1}H and ^{13}C NMR data. Spectral data, however, while being consistent in each case with a single geometrical isomer, did not allow assignment of a definite cis or trans stereochemistry. Moreover, spectral data did not allow us to ascertain whether each compound occurred as a single tautomeric form or as a mixture of the two possible tautomers. Subsequent X-ray crystallographic analysis of the benzylated cyanopyrrolopyrrole **10d** and the corresponding cyanopyrrolopyridine **11c** established the actual trans stereochemistry for both compounds.[18] Crystallographic analysis also proved that pyrrole **10d** occurred as a mixture of the two tautomers, whereas pyridine **11c** was present as a single form bearing the tautomeric hydrogen on the pyridine nitrogen. On this basis, the trans stereochemistry was generally assumed for all compounds **10** and **11**; additionally, compounds **10** were assumed to occur as

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(12) Montevecchi, P. C.; Navacchia, M. L.; Spagnolo, P. *J. Org. Chem.* **1997**, *62*, 5846−5848.

(13) For very recent examples of carbon radical cyclizations onto nitriles and their use in synthesis, see: (a) Bowman, W. R.; Bridge, C. F.; Brookes, P. *Tetrahedron Lett.* **2000**, *41*, 8989−8994. (b) Bowman, W. R.; Bridge, C. F.; Cloonan, M. O.; Leach, D. C. *Synlett* **2001**, 765−768. (c) Bowman, W. R.; Bridge, C. F.; Brookes, P.; Cloonan, M. O.; Leach, D. C *J. Chem. Soc., Perkin Trans. 1* **2002**, 58−68.

(14) Diez-Barra, E.; De La Hoz, A.; Moreno, A.; Sanchez-Verdù, P. *J. Chem. Soc., Perkin Trans. 1* **1991**, 2589−2592.

(15) Orita, A.; Hasegawa, D.; Nakamo, T.; Otera, J. *Chem. Eur. J.* **2002**, *8*, 2000−2004.

(16) Products **3**, **5**, **9**, and **16** can exist as two tautomers. Calculations suggest that the aminic form could be the preferred one (see Supporting Information).

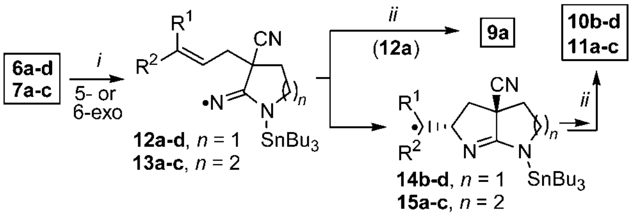
(17) Amidines are known to be formed by addition of amines to nitriles; see: Smith, M. B.; March, J. In *Advanced Organic Chemistry*−*Reactions, Mechanisms and Structures*, 5th ed.; Wiley-Interscience: New York, 2001; pp 1191−1192.

(18) See Supporting Information for the X-ray analyses of **10d** and **11c**.

tautomeric mixtures, while compounds **11** were assumed to occur as single tautomers (Figure 2).

The bulk of chemical evidence provided by the present radical reactions of azidonitriles **6a−d**, **7a−c**, and **8** would lead to the conclusion that the derived stannylaminyl radicals could normally undergo highly efficient addition onto a cyano group in both 5-exo and, even more interestingly, 6-exo fashion, yielding aminoiminyl radicals **12** and **13**. The 5-exo cyclized iminyl radical **12a** avoided subsequent cyclization onto the allylic moiety and exhibited only reduction to amidine **9a** (Table 1, entry 5 and Scheme 2).

Scheme 2[a]



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

On the contrary, the other 5- and 6-exo cyclized iminyl radicals **12b−d** and **13a−c** generally exhibited 5-exo cyclization onto their alkenyl substituent yielding the eventual products **10b−d** and **11a−c**. The tandem processes, however, were found to occur to an extent increasing on passing from **12b** to **12c**,**d** and, similarly, from **13a** to **13b**,**c** (Table 1, entries 5−8 and 9−11). It therefore appears that the feasibility of the tandem cyclization is highly dependent on the stability of the ensuing C-centered radicals **14** and **15** (Scheme 2).

It is worth noting that the stereochemistry of compounds **10b−d** and **11a−c** was also correctly predicted by using the Beckwith−Houk models for the transition states of 5-exo cyclizations (see Supporting Information).[1b] This result, together with a very small calculated energy difference between radicals *cis*-**14b** and *trans*-**14b** (−1.1 kcal/mol, DFT, $SnBu_3 = SnMe_3$) suggests that ring closure of aminoiminyls could occur under kinetic control and could be substantially irreversible.

As for the 5-exo cyclized iminyl radical derived from azide **8**, the observed failure to undergo possible 6-exo cyclization onto the alkenyl moiety to give a pyrrolopyridine in favor of exclusive reduction to pyrrolidinimine **16** (Figure 2) was likely a consequence of the lower feasibility of 6-exo cyclization than 5-exo cyclization, which is usually the case in radical chemistry.

It is noteworthy that the stannylaminyl radicals derived from azides **6b−d** and **7a−c** provided diagnostic evidence for neither H-abstraction from the tin hydride nor (**6b−d**) 1,5-H transfer from the allylic positions of their alkenylic chains.

In conclusion, stannylaminyl radicals derived from azides can perform highly efficient cyclization onto a cyano group in both 5- and 6-exo fashion. The fair reactivity of stannylaminyl radicals toward nitrile groups should be largely due to both their nucleophilic nature, which would favor attack to the electrophilic nitrile carbon,[19] and, more importantly, to the consequent production of aminoiminyl radicals, which would be stabilized species as a result of resonance delocalization of the amino lone pair.[20] In fact, these iminyls did not bring about any 1,4- or 1,5-nitrile translocations, in sharp contrast to the alkyl/aryl-substituted congeners.[13a,21] The cyclized aminoiminyl radicals can interestingly exhibit 5-exo cyclization onto an internal alkene, thus offering a new valuable entry to pyrrolopyrroles and pyrrolopyridines.

Studies are still in progress to further understand the reactivity of stannylaminyl radical cyclization onto nitriles as well as its potential in heterocyclic synthesis.

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Supporting Information Available: Experimental procedures for the synthesis of azidonitriles and their radical reactions; spectral data for all new compounds; X-ray diffraction details, as well as CIF files, for compounds **10d** and **11c**; TS models for cyclization of **12d**; and optimized (DFT) structures of *cis*- and *trans*-**14b**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(19) In malononitriles the concomitant presence of two CN groups on the same carbon is expected to enhance the electrophilicity of both groups. This might play a further role in favoring cyclization of the nucleophilic stannylaminyl radical onto either nitrile group of our azidomalononitriles.

(20) Thermodynamic and structural data for 1-amino-substituted iminyl radicals are not available in the literature.

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