# Iminyl Radicals from α-Azido *o*-Iodoanilides via 1,5-H Transfer Reactions of Aryl Radicals: New Transformation of α-Azido Acids to Decarboxylated Nitriles

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R = H, Me, *n*-C$_{11}$H$_{23}$, 1-adamantyl,
PhCH$_2$, (3-indolyl)CH$_2$
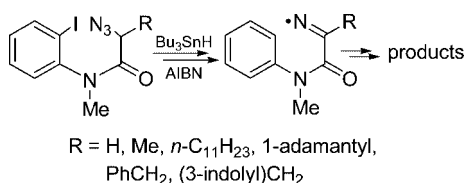
The radical reaction of tributyltin hydride with *o*-iodo-*N*-methylanilides derived from α-azido acids provides an excellent access to α-(aminocarbonyl)iminyl radicals through 1,5-hydrogen transfer reaction of initially formed aryl radicals followed by β-elimination of dinitrogen from ensuing α-azido-α-(aminocarbonyl)alkyl radicals. The outcoming iminyls display a peculiar tendency to form corresponding nitriles by β-elimination of aminocarbonyl radicals.

In recent years considerable attention has been devoted to the radical chemistry of alkyl and aryl azides, which have been shown to act, to a varying degree, as radical acceptors toward a range of carbon- and heteroatom-centered species yielding aminyl radicals after nitrogen loss from initial triazenyl adducts.[1] The intramolecular additions of carbon radicals usefully afford cyclic aminyl radicals that are valuable intermediates for the synthesis of *N*-heterocycles.[2] The intermolecular additions of silyl,[3a] germyl,[3b] indyl,[3c] and, mainly, stannyl radicals[1] efficiently lead to corresponding *N*-substituted aminyl radicals. In particular, *N*-stannylaminyl

radicals are the key intermediates in many azide cyclization/rearrangement processes mediated by tributyltin hydride (Bu$_3$SnH) and AIBN.[1,4]

The radical chemistry of azides has invariably been confined to the generation and synthetic applications of aminyl radicals, although a work appeared in 1997 seemingly suggesting that alkyl azides might additionally act as progenitors of iminyl radicals, provided that transient radicals be produced on the carbon atom linked to the azido function.[5] The radical chain reaction of benzenethiol with α-azidostyrenes was found to afford virtually quantitative yields of β-sulfanylated imines and tautomeric enamines clearly ascribable to the intervention of 2-sulfanyliminyl radicals. These intermediates could result from sulfanyl radical attack at the azide β-carbon followed by β-elimination of molecular nitrogen from the ensuing α-azido-benzyl radical adduct.[5] Surprisingly, despite that promising chemical information, the potential utility of alkyl azides in the production of iminyl radicals has remained to date totally ignored.

Iminyl radicals are of significant interest in synthetic radical chemistry due to their ability to perform cyclizations onto aromatic rings[6a,e,f] and double bonds,[7] and additional fragmentation reactions to give nitrile products.[5,7b,8] These nitrogen species have been formerly generated by various methods, i.e., thermolysis, photolysis, or flash vacuum pyrolysis of *N*-substituted imine derivatives,[6a–d] intramolecular addition of carbon[6e,f,8b,c] and nitrogen radicals[4g] to nitriles, and radical-chain reactions of Bu$_3$SnH with sulfanylimines,[9a] benzotriazolylimines,[8a] and xanthic hydrazones.[9b,c]

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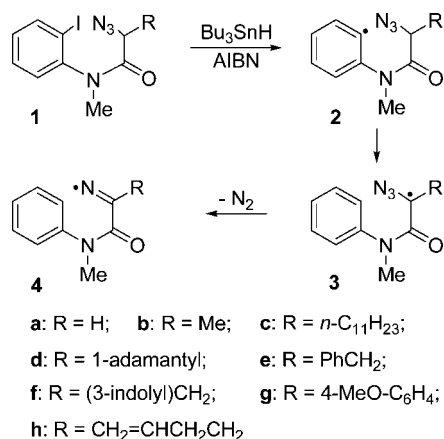
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SCHEME 1

a: R = H;   b: R = Me;   c: R = *n*-C$_{11}$H$_{23}$;

d: R = 1-adamantyl;   e: R = PhCH$_2$;

f: R = (3-indolyl)CH$_2$;   g: R = 4-MeO-C$_6$H$_4$;

h: R = CH$_2$=CHCH$_2$CH$_2$

In previous studies it has been shown that the radical reaction of Bu$_3$SnH/AIBN with *N*-substituted *o*-iodoanilides results in smooth generation of the carbon radicals adjacent to the carbonyl group via 1,5-hydrogen transfer reactions of the initially formed aryl radicals.[10] In light of these interesting findings, we reasoned that analogous *o*-iodoanilides bearing an azido function on the carbon attached to the carbonyl group should similarly provide an easy entry to corresponding α-azidoalkyl radicals, which might probably form iminyl radicals by subsequent elimination of molecular nitrogen. We were therefore led to prepare several α-azido *o*-iodo-*N*-methylanilides (**1a−h**) in order to ascertain the possible synthetic potential of their radical reactions with Bu$_3$SnH for the generation of the corresponding iminyl radicals **4a−h** (Scheme 1). In view of previous evidence,[2c,f] we expected that, in the presence of the azido moiety, stannyl radicals should perform selective iodine abstraction to give initial aryl radicals **2a−h**.

The hitherto unknown substrates **1a−h** were readily available with standard methodology. In particular, compounds **1a−d** were obtained by treatment of *o*-iodo-*N*-methylaniline with the appropriate α-bromoalkanoyl bromide/chloride followed by treatment of the resultant bromoanilide with sodium azide in DMSO. The azido compounds **1e−h** were similarly obtained, but in these cases the iodoaniline was reacted with preliminary α-azido acyl chlorides.

The reactions between our azido iodoanilides (0.5 mmol) and Bu$_3$SnH (0.75 mmol) were usually carried out in refluxing benzene (50 mL) and were initiated by thermal decomposition of AIBN (0.125 mmol). The reactions were prolonged until complete disappearance of the starting material (4−5 h) and the crude mixtures were then directly subjected to chromatographic separation. Anilides **1c−e** invariably furnished high yields of the respective fragmented nitrile, namely dodecanenitrile **6c**, 1-adamantanecarbonitrile **6d**, and phenylacetonitrile **6e**, along with a comparable amount of formanilide **5**. Compound **1c** additionally furnished a modest amount of 3-undecylquinoxalinone **7c**, while the congeners **1d,e** virtually failed to form the corresponding cyclized products **7d,e** (Scheme 2 and Table 1, entries 3−5). (3-Indolyl)propionamide **1f** similarly led to major production of (3-indolyl)acetonitrile **6f** and formamide **5**, but, in this case, minor
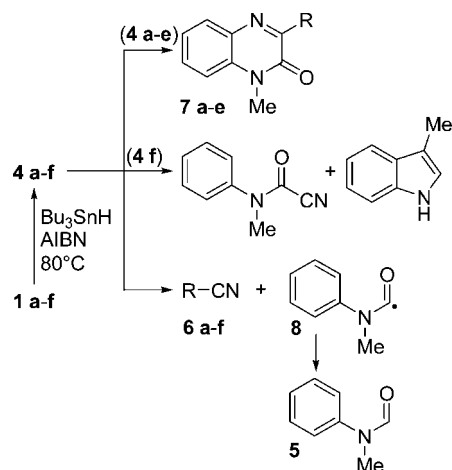
SCHEME 2

TABLE 1. Radical Reactions of Azidoanilides **1a−f** with Bu$_3$SnH/AIBN in Refluxing Benzene

		products (%)^a		
entry	anilide	5	6	7
1	**1a**	55	—^{b}	15
2	**1b**	60	—^{c}	18
3	**1c**	65	75	20
4	**1d**	84	86	<2
5	**1e**^{d}	89	80	<2
6	**1f**^{e}	45	50	
7	**1c**^{f}	80	85	13

^{a} Yields isolated by column chromatography. ^{b} Hydrogen cyanide **6a** was not detected. ^{c} Acetonitrile **6b** was not detected. ^{d} Trace amounts of *N*-methyl-*N*-phenylcarbamoyl cyanide were also isolated. ^{e} 3-Methylindole (18%) and *N*-methyl-*N*-phenylcarbamoyl cyanide (17%) were also isolated (see text). ^{f} Reaction carried out at 110 °C.

production of *N*-methyl-*N*-phenylcarbamoyl cyanide and 3-methylindole additionally occurred (Scheme 2 and Table 1, entry 6).

Further, an analogous behavior was encountered with acetanilide **1a** and propionanilide **1b**, since both compounds gave a fairly good yield of the usual formanilide **5** together with minor amounts of oxoquinoxalines **7a,b**. Under these circumstances, however, the presumable nitrilic products, i.e., hydrogen cyanide **6a** and acetonitrile **6b**, respectively, escaped detection (Scheme 2 and Table 1, entries 1 and 2).

The encountered products evidently pointed to the actual intervention of the desired iminyl radicals **4a−f**. Despite our reductive conditions, these radicals **4** were essentially prone to undergo β-fragmentation to yield nitrile **6** and carbamoyl radical **8**,[11] and thence formanilide **5**, as well as, but to a (very) limited extent, competing aromatic cyclization to oxoquinoxaline **7**.[12] However, iminyl **4f** was also somewhat prone to afford *N*-methyl-*N*-phenylcarbamoyl cyanide and 3-methylindole by an alternative β-elimination of (3-indolyl)methyl radical.[13]

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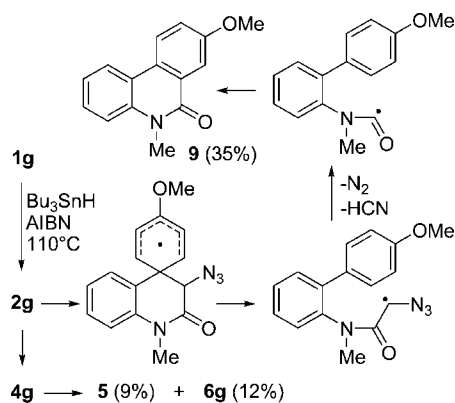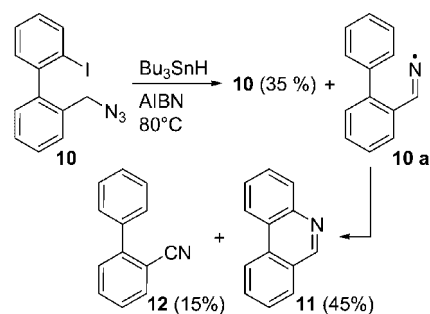
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(12) For recent mechanistic discussion on homolytic aromatic cyclizations in the presence of Bu$_3$SnH, see:(a) Beckwith, A. L. J.; Bowry, V. W.; Bowman, W. R.; Mann, E.; Parr, J.; Storey, J. M. D. *Angew. Chem., Int. Ed.* **2004**, *43*, 95. (b) Bowman, W. R.; Storey, J. M. D. *Chem. Soc. Rev* **2007**, *36*, 1803.

(13) This mechanism apparently occurred to a minute extent also with iminyl radical **4e**, as suggested by isolation of trace amounts of *N*-methyl-*N*-phenylcarbamoyl cyanide from the reaction of anilide **1e**.

SCHEME 3

SCHEME 4

of carbamoyl radical **8** forming the corresponding nitrile **6**. Notably, the preferential release of radical **8** was irrespective of the stability of the alkyl radical that might have been alternatively expelled.[15,16] Such peculiar behavior of iminyls **4** was rather unpredictable since it was still unknown that carbamoyl radical **8** would be more stable even than fairly stabilized alkyl radicals. Consequently, in view of the easy availability of α-azido acids by various established methods,[1d,17] we were led to discover that the present anilides **1** can find interesting use in the unprecedented radical conversion of those azido acids into decarboxylated alkanenitriles.

In this work we also performed a brief investigation of the radical reactivity of another accessible alkyl azide, i.e., the iodo azide **10** shown in Scheme 4. Under our standard conditions, the progressive consumption of **10** was noticeably low, probably due to poorly efficient chain reaction with stannyl radicals.[18] Much unaltered material **10** (35%) was recovered even after prolonging the reaction time for 16 h and concomitantly using a double amount of AIBN. However, clean evidence was obtained that also under these circumstances tandem hydrogen translocation and dinitrogen extrusion offer an excellent entry to iminyl radical **10a**. In fact, phenanthridine **11** (45%) and nitrile **12** (15%)[19] were found to occur as the virtually exclusive reaction products (Scheme 4).

In conclusion, *o*-iodo-*N*-methylanilides derived from α-azido acids can act as excellent precursors of novel α-(aminocarbonyl)iminyl radicals through very fast 1,5-hydrogen transfer reaction of the initial aryl radicals and subsequent extrusion of dinitrogen by the ensuing α-azidoalkyl radicals. Those iminyl radicals have a peculiar tendency to form the corresponding nitrile by β-elimination of carbamoyl radical and therefore can be exploited for a new radical transformation of α-azido acids into decarboxylated nitriles. Regardless of the present mechanistic and synthetic implications, this work has clearly established that alkyl azides can be envisioned as powerful precursors not only of aminyl radicals but also of the iminyl congeners. This fact could lead to rewarding future applications to synthetic radical chemistry.

These observations prompted us to prove that under more forcing thermal conditions the production of nitrile **6** might conceivably be improved at the expense of quinoxaline **7**. Indeed, when the reaction of tridecanamide **1c** was repeated at 110 °C in a sealed tube, the outcoming yield of dodecanenitrile **6c** (and **5**) was usefully enhanced at the expense of **7c** (Table 1, entries 3 and 7). In light of this rewarding finding the behavior of the additional (4-methoxyphenyl)acetanilide **1g** was directly examined at 110 °C. Unexpectedly, compound **1g** failed to act as an efficient source of iminyl radical **4g**, since it actually led to a rather complex reaction mixture from which phenanthridone **9** was isolated in 35% yield along with only poor amounts of 4-methoxybenzonitrile **6g** and formanilide **5** (Scheme 3). The observed phenanthridone **9** was presumably formed through the impressive cascade radical process outlined in Scheme 3. For curious reasons, the derived aryl radical **2g** was seriously discouraged to undergo 1,5-H transfer in favor of six-membered ipso-cyclization onto the adjacent aromatic ring, despite the fact that in this case the H-transfer process might have been especially promoted by the generation of fairly stable azidobenzylic radical **3g**.

Our final attempt to study 2-azido-5-hexenanilide **1h** was unfortunately frustrated by the finding that this unsaturated azide, under our standard conditions, suffered fairly rapid decomposition, probably owing to intramolecular cycloaddition onto the alkene moiety.

Thus, the general chemical evidence furnished by the above findings strictly suggests that anilides **1**, except when an aryl was present on the α-carbon, were able to cleanly afford the respective α-(aminocarbonyl)iminyl radicals **4**[14] via very fast 1,5-hydrogen transfer of primary aryl radicals **2** followed by rapid extrusion of dinitrogen from the resultant azidoalkyl radicals **3** (Scheme 1). This fact was further substantiated by our general failure to observe any deiodinated substrate, which might have resulted from tin hydride reduction of aryl radical **2** and/or translocated azidoalkyl radical **3**. The resulting iminyl radicals **4**, besides displaying a certain ability to give 6-membered aromatic cyclization onto the adjacent anilide ring, revealed a fair propensity to undergo selective β-elimination

(14) To the best of our knowledge no previous instances of α-(aminocarbonyl)iminyl radicals are available in the literature. The chemistry of other α-carbonyl-substituted analogues is virtually unknown, but recent chemical and/or spectral evidence would indicate that α-benzoyliminyl radical undergoes rapid fragmentation into benzoyl radical and a nitrile at temperatures exceeding −60 °C, whereas the α-fluoroformyl counterpart is relatively stable, see:(a) Groenenboom, C. J.; Hageman, H. J.; Oosterhoff, P.; Overeem, T.; Verbeck, J. *J. Photochem. Photobiol. A* **1997**, *107*, 261. (b) Bucher, G.; Kolano, C.; Schade, O.; Sander, W. *J. Org. Chem.* **2006**, *71*, 2135.

(15) In the case of iminyl **4f**, alternative fragmentation at the alkyl side could be somewhat promoted by the notable stability of the released (3-indolyl)methyl radical.

(16) The observed preference of iminyl radical **4** for β-fragmentation over intramolecular cyclization to oxoquinoxaline **7** was seemingly enhanced by the bulkyness of the adjacent R substituent (see Table 1).

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Experimental Section

Radical Reactions of Azido Anilides 1 with Tributyltin Hydride: General Procedure. A solution of azido anilide **1** (0.5 mmol) and tributyltin hydride (0.75 mmol) in benzene (50 mL) containing AIBN (0.06 mmol) was refluxed for ca. 1.5 h; after a further addition of AIBN (0.06 mmol), the reaction mixture was refluxed for an additional 2−3 h (until TLC monitored the absence of any starting material). After cooling, the excess solvent was removed in vacuo and the residue was subjected to chromatographic separation on silica gel by gradual elution with light petroleum/diethyl ether mixtures and final elution with dichloromethane or methanol. The reactions of anilides **1c** and **1g** at 110 °C were performed in a similar fashion, but the respective benzene mixtures were allowed to react in a sealed tube immersed in an oil bath kept at 110 °C. Yields of the isolated products are reported in Table 1 and Scheme 3.

Supporting Information Available: Experimental procedures for the preparation of azides **1a−h** and **10** and their radical reactions with Bu₃SnH; characterization data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(18) Tin radicals were probably destroyed to a certain extent through H-abstraction reaction with those cyclohexadienyl radicals that arose from intramolecular addition of **10a** onto the adjacent aromatic ring.

(19) Nitrile **12** was presumably the result of a β-hydrogen-atom abstraction mechanism operating on iminyl radical **10a**.